Closing Argument

Roadmap

- Infringement → Pacira's burden: **Preponderance of the Evidence**

- Invalidity
  - Obviousness
  - Anticipation
  - Enablement
- Inequitable Conduct

} Defendants' burden: **Clear and Convincing Evidence**

Defendants Infringe

Asserted Claim 7 of the ’495 Patent

7. A composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising:
(a) mixing a first aqueous solution comprising phosphoric acid with a volatile water-immiscible solvent solution to form a water-in-oil first emulsion, wherein the volatile water-immiscible solvent solution comprises bupivacaine, 1, 2-dierucoylphosphatidylcholine (DEPC), 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), and at least one neutral lipid;
(b) mixing the water-in-oil first emulsion with a second aqueous solution to form a water-in-oil-in-water second emulsion, wherein the second aqueous solution comprises lysine and dextrose;
(c) removing the volatile water-immiscible solvent from the water-in-oil-in-water second emulsion to form a first aqueous suspension of bupivacaine encapsulated MVLs having a first volume;
(d) reducing the first volume of the first aqueous suspension of bupivacaine encapsulated MVLs by microfiltration to provide a second aqueous suspension of bupivacaine encapsulated MVLs having a second volume;
(e) exchanging the aqueous supernatant of the second aqueous suspension with a saline solution by diafiltration to provide a third aqueous suspension of bupivacaine encapsulated MVLs having a third volume; and
(f) further reducing the third volume of the third aqueous suspension by microfiltration to provide a final aqueous suspension of bupivacaine encapsulated MVLs having a target concentration from about 12.6 mg/mL to about 17.0 mg/mL;
wherein all steps are carried out under aseptic conditions; and
wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25° C. for one month.
wherein the erucic acid concentration in the composition is about 99 µg/mL or less after the composition is stored at 25° C. for six months.

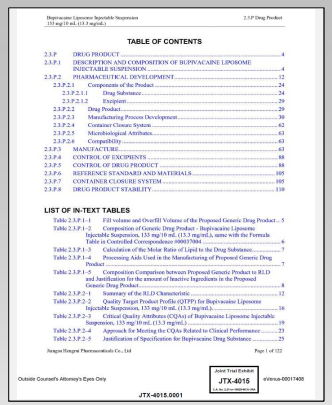
Defendants Infringe

- "[I]f a product that an ANDA applicant is asking the FDA to approve for sale falls within the scope of an issued patent, a judgment of infringement must necessarily ensue."

  -*Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013)

- Defendants' stability specification for erucic acid (NMT 250 µg/mL) encompasses the contested claim limitations

Defendants' ANDA Clearly Addresses Erucic Acid at Accelerated Conditions



JTX-4015 (10mL 2.3.P Drug Product) at JTX-4015.0001

Bupivacaine Liposome Injectable Suspension
133 mg/10 mL (13.3 mg/mL)

2.3.P Drug Product

TABLE OF CONTENTS

See also JTX-4038 (20mL 2.3.P Drug Product) at JTX-4038.0278-279, 284

Defendants' ANDA Clearly Addresses Erucic Acid at Accelerated Conditions, Even Calling it a "Specification"

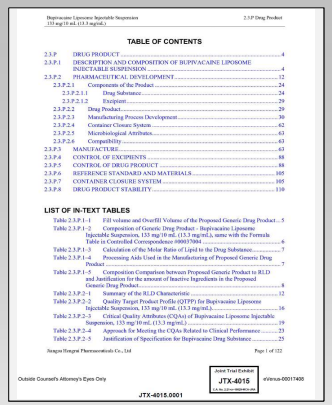


TABLE OF CONTENTS

2.3.P DRUG PRODUCT 4
2.3.P.1 DESCRIPTION AND COMPOSITION OF BUPIVACAINE LIPOSOME INJECTABLE SUSPENSION 4
2.3.P.2 PHARMACEUTICAL DEVELOPMENT 12
2.3.P.2.1 Components of the Product 24
2.3.P.2.1.1 Drug Substance 24
2.3.P.2.1.2 Excipient 29
2.3.P.2.2 Drug Product 29
2.3.P.2.3 Manufacturing Process Development 30
2.3.P.2.4 Container Closure System 62
2.3.P.2.5 Microbiological Attributes 63
2.3.P.2.6 Compatibility 63
2.3.P.3 MANUFACTURE 63
2.3.P.4 CONTROL OF EXCIPIENTS 88
2.3.P.5 CONTROL OF DRUG PRODUCT 88
2.3.P.6 REFERENCE STANDARD AND MATERIALS 105
2.3.P.7 CONTAINER CLOSURE SYSTEM 105
2.3.P.8 DRUG PRODUCT STABILITY 110

LIST OF IN-TEXT TABLES

Table 2.3.P.1-1 Fill volume and Overfill Volume of the Proposed Generic Drug Product 5
Table 2.3.P.1-2 Composition of Generic Drug Product - Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL (13.3 mg/mL), same with the Formula Table in Controlled Correspondence #00037080 6
Table 2.3.P.1-3 Calculation of the Molar Ratio of Lipid to the Drug Substance 7
Table 2.3.P.1-4 Processing Aids Used in the Manufacturing of Proposed Generic Drug Product 7
Table 2.3.P.1-5 Composition Comparison between Proposed Generic Product to RLD and Justification for the amount of Inactive Ingredients in the Proposed Generic Drug Product 8
Table 2.3.P.2-1 Summary of the RLD Characteristic 12
Table 2.3.P.2-2 Quality Target Product Profile (QTPP) for Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL (13.3 mg/mL) 16
Table 2.3.P.2-3 Critical Quality Attributes (CQAs) of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL (13.3 mg/mL) 19
Table 2.3.P.2-4 Approach for Meeting the CQAs Related to Clinical Performance 23
Table 2.3.P.2-5 Justification of Specification for Bupivacaine Drug Substance 25

Hospira Hospital Pharmaceuticals Co., Ltd Page 1 of 122

Outside Counsel's Attorney's Eyes Only

Joint Trial Exhibit JTX-4015 For Joint Trial Use Only

eVersa-00017400

JTX-4015.0001

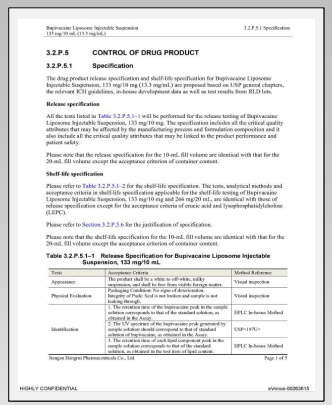
JTX-4015 (10mL 2.3.P Drug Product) at JTX-4015.0111-.0112

Table 2.3.P.8–1. Specification for Stability Study

Tests	Method Reference	Acceptance Criteria (for Release)	Acceptance Criteria (for Stability)
Erucic acid	HPLC In-house Method	NMT 100 µg/mL	NMT 250 µg/mL

See also JTX-4038 (20mL 2.3.P Drug Product) at JTX-4038.0278-279, 284

Defendants' ANDA Clearly Addresses Erucic Acid at Accelerated Conditions, Even Calling it a "Specification"



JTX-4027 (10 mL 3.2.P.5.1 Specification) at JTX-4027.0001

Bupivacaine Liposome Injectable Suspension
133 mg/10 mL (13.3 mg/mL)

3.2.P.5.1 Specification

3.2.P.5 CONTROL OF DRUG PRODUCT

3.2.P.5.1 Specification

The drug product release specification and shelf-life specification for Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg (13.3 mg/mL) are proposed based on USP general chapters, the relevant ICH guidelines, in-house development data as well as test results from RLD lots.

Release specification

All the tests listed in Table 3.2.P.5.1–1 will be performed for the release testing of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg. The specification includes all the critical quality attributes that may be affected by the manufacturing process and formulation composition and it also include all the critical quality attributes that may be linked to the product performance and patient safety.

Please note that the release specification for the 10-mL fill volume are identical with that for the 20-mL fill volume except the acceptance criterion of container content.

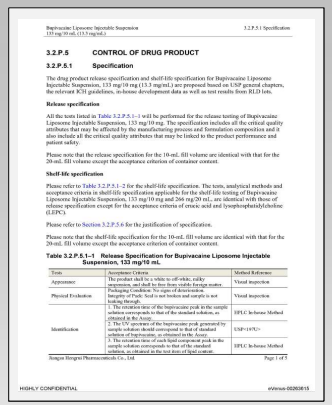
Shelf-life specification

Please refer to Table 3.2.P.5.1–2 for the shelf-life specification. The tests, analytical methods and acceptance criteria in shelf-life specification applicable for the shelf-life testing of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg and 266 mg/20 mL, are identical with those of release specification except for the acceptance criteria of erucic acid and lysophosphatidylcholine (LEPC).

Please refer to Section 3.2.P.5.6 for the justification of specification.

Please note that the shelf-life specification for the 10-mL fill volume are identical with that for the 20-mL fill volume except the acceptance criterion of container content.

Defendants' ANDA Clearly Addresses Erucic Acid at Accelerated Conditions, Even Calling it a "Specification"



3.2.P.5 CONTROL OF DRUG PRODUCT

3.2.P.5.1 Specification

The drug product release specification and shelf-life specification for Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg (13.3 mg/mL) are proposed based on USP general chapters, the relevant ICH guidelines, in-house development data as well as test results from RLD lots.

Release specification

All the tests listed in Table 3.2.P.5.1–1 will be performed for the release testing of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg. The specification includes all the critical quality attributes that may be affected by the manufacturing process and formulation composition and it also include all the critical quality attributes that may be linked to the product performance and patient safety.

Please note that the release specification for the 10-mL fill volume are identical with that for the 20-mL fill volume except the acceptance criterion of container content.

Shelf-life specification

Please refer to Table 3.2.P.5.1–2 for the shelf-life specification. The tests, analytical methods and acceptance criteria in shelf-life specification applicable for the shelf-life testing of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mg and 266 mg/20 mL, are identical with those of release specification except for the acceptance criteria of erucic acid and lysophosphatidylcholine (LEPC).

Please refer to Section 3.2.P.5.6 for the justification of specification.

Please note that the shelf-life specification for the 10-mL fill volume are identical with that for the 20-mL fill volume except the acceptance criterion of container content.

Table 3.2.P.5.1–1 Release Specification for Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL

Tests	Acceptance Criteria	Method Reference
Appearance	The product shall be a white to off-white, milky suspension, and shall be free from visible foreign matter.	Visual inspection
Physical Evaluation	Integrity of Pseudomonic Acid is not broken and sample is not leaking through.	Visual inspection
Identification	1. The retention time of the bupivacaine peak in the sample solution corresponds to that of the standard solution, as obtained in the Assay.	HPLC In-house Method
	2. The UV spectrum of the bupivacaine peak generated by sample solution should correspond to that of standard solution of bupivacaine, as obtained in the Assay.	USP<197>
	3. The retention time of each lipid component peak in the sample solution corresponds to that of the standard solution, as obtained in the test item of lipid content.	HPLC In-house Method

Ningxia Hengrui Pharmaceuticals Co., Ltd. Page 1 of 5

HIGHLY CONFIDENTIAL eVimm-00260815

JTX-4027 (10 mL 3.2.P.5.1 Specification) at JTX-4027.0002-.0003

Table 3.2.P.5.1–2 Shelf-life Specification for Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL

Tests	Acceptance Criteria	Method Reference
Particulate matter	Does not exceed 6000 per container equal to or greater than 10 µm and does not exceed 600 per container equal to or greater than 25 µm.	USP<788> Method 1
Bacterial Endotoxins*	Less than 15 EU per mL of Bupivacaine Liposome Injectable Suspension.	USP <85> Gel-clot Technique
Sterility	No evidence of microbial growth.	USP <71> Direct Inoculation of the Culture Medium
Osmolality	260 - 330 mOsmol/kg	USP <785>
pH of IAP (internal aqueous phase)	4.70 – 5.38	USP <791>
Osmolality of IAP (internal aqueous phase)	260 - 330 mOsmol/kg	USP <785>
Packed Particle Volume (PPV)	31.0%~42.0%	In-house Method
Residual Solvents*	Methylene chloride: NMT 300 ppm.	USP <467>
Erucic Acid	NMT 250 µg/mL	HPLC In-house Method

Defendants' ANDA Clearly Addresses Erucic Acid at Accelerated Conditions, Even Calling it a "Specification"

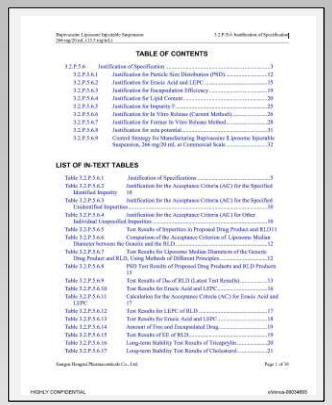


TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

JTX-4026 (20mL 3.2.P.5.6 Justification of Specification) at JTX-4026.0004, .0008

Table 3.2.P.5.6.1 Justification of Specifications

Tests	Acceptance Criteria	Consideration of the Establishment of Acceptance Criteria
Erucic acid	Release: NMT 100 µg/mL. Stability: NMT 250 µg/mL.	Based on test results of our proposed drug product and RLD, the erucic acid may be introduced by excipients DEPC, the release specification is set to NMT 100 µg/mL; The concept "significant change" in ICH Q1A is adopted to set the stability acceptance criteria. When content of DEPC significant depredate by 5%, the content of erucic acid increase by about 155 µg/mL, therefore, the stability specification is set to be NMT 250 µg/mL. Both the acceptance criteria for release (100 µg/mL) and stability (250 µg/mL) are far less than the PDE value of 17.5 mg/mL. Please refer to Section 3.2.P.5.6.2 for details.

See also PTX-081 (10mL 3.2.P.5.6 Justification of Specification) at PTX-081.0004-8

Defendants' ANDA Clearly Addresses Erucic Acid at Accelerated Conditions, Even Calling it a "Specification"

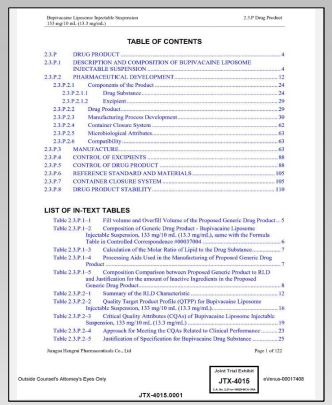


TABLE OF CONTENTS

2.3.P DRUG PRODUCT 4
2.3.P.1 DESCRIPTION AND COMPOSITION OF BUPIVACAINE LIPOSOME INJECTABLE SUSPENSION 4
2.3.P.2 PHARMACEUTICAL DEVELOPMENT 12
2.3.P.2.1 Components of the Product 24
2.3.P.2.1.1 Drug Substance 24
2.3.P.2.1.2 Excipient 29
2.3.P.2.2 Drug Product 29
2.3.P.2.3 Manufacturing Process Development 30
2.3.P.2.4 Container Closure System 62
2.3.P.2.5 Microbiological Attributes 63
2.3.P.2.6 Compatibility 63
2.3.P.3 MANUFACTURE 63
2.3.P.4 CONTROL OF EXCIPIENTS 88
2.3.P.5 CONTROL OF DRUG PRODUCT 88
2.3.P.6 REFERENCE STANDARD AND MATERIALS 105
2.3.P.7 CONTAINER CLOSURE SYSTEM 105
2.3.P.8 DRUG PRODUCT STABILITY 110

LIST OF IN-TEXT TABLES

Table 2.3.P.1-1 Fill volume and Overfill Volume of the Proposed Generic Drug Product 5
Table 2.3.P.1-2 Composition of Generic Drug Product - Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL (13.3 mg/mL), same with the Formula Table is Controlled Correspondence #00037080 6
Table 2.3.P.1-3 Calculation of the Molar Ratio of Lipid to the Drug Substance 7
Table 2.3.P.1-4 Processing Aids Used in the Manufacturing of Proposed Generic Drug Product 7
Table 2.3.P.1-5 Composition Comparison between Proposed Generic Product to RLD and Justification for the amount of Inactive Ingredients in the Proposed Generic Drug Product 8
Table 2.3.P.2-1 Summary of the RLD Characteristic 12
Table 2.3.P.2-2 Quality Target Product Profile (QTPP) for Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL (13.3 mg/mL) 16
Table 2.3.P.2-3 Critical Quality Attributes (CQAs) of Bupivacaine Liposome Injectable Suspension, 133 mg/10 mL (13.3 mg/mL) 19
Table 2.3.P.2-4 Approach for Meeting the CQAs Related to Clinical Performance 23
Table 2.3.P.2-5 Justification of Specification for Bupivacaine Drug Substance 25

Ningxia Hengrui Pharmaceuticals Co., Ltd Page 1 of 122

Outside Counsel's Attorney's Eyes Only

Joint Trial Exhibit JTX-4015 For Case 2:21-cv-19829-MCA-JRA

eVerus-00017400

JTX-4015.0001

JTX-4015 (10mL 2.3.P Drug Product) at JTX-4015.0111-.0112, .0116

Table 2.3.P.8–1. Specification for Stability Study

Tests	Method Reference	Acceptance Criteria (for Release)	Acceptance Criteria (for Stability)
Erucic acid	HPLC In-house Method	NMT 100 µg/mL	NMT 250 µg/mL

Table 2.3.P.8–2. Stability Information of the Three ANDA Submission Batches

Fill volume	Package Configuration	Batch No.	Test Condition	Storage Orientation	Test Schedule
10 mL	Same as the package intended for marketing	210401BM	Long-term (5°C ± 3°C)	Upright/Inverted	Initial, 3, 6 months
			Accelerated (25°C ± 2°C/60% RH ± 5% RH)	Upright/Inverted	Initial, 1, 2, 3, 6 months
		210425BM	Long-term (5°C ± 3°C)	Upright/Inverted	Initial, 3, 6 months
			Accelerated (25°C ± 2°C/60% RH ± 5% RH)	Upright/Inverted	Initial, 1, 2, 3, 6 months
		210527BM	Long-term (5°C ± 3°C)	Upright/Inverted	Initial, 3, 6 months
			Accelerated (25°C ± 2°C/60% RH ± 5% RH)	Upright/Inverted	Initial, 1, 2, 3, 6 months

See also JTX-4038 (20mL 2.3.P Drug Product) at JTX-4038.0278-279, 284

Defendants Applied Their Specification to Accelerated Stability Testing

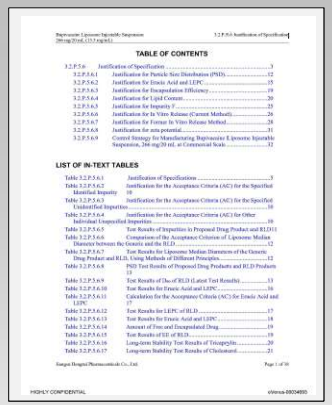


TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

JTX-4029 (10mL 3.2.P.8.3 Stability Data) at JTX-4029.0050-.0051

Bupivacaine Liposome Injectable Suspension
133 mg/10 mL (13.3 mg/mL)

3.2.P.8.3 Stability Data

Table 3.2.P.8.3.2–3. Upright **Test Results for Accelerated Stability Study (Batch 210425BM) at 25°C ± 2°C/60% RH ± 5% RH,**

Drug Product Name/ strength	Bupivacaine Liposome Injectable Suspension (strength: *133 mg/10 mL (13.3 mg/mL)*)	Protocol No.	DP-P08-Y04-17026 03
Container closure system	Same as the package intended for marketing	Start time	Apr. 26th, 2021
Manufacture date	Apr. 25th, 2021	Storage condition	25°C ± 2°C/60%RH±5% RH
Batch number/batch size (Actual output)	210425BM/6808 vials	Placement method	Upright

Sampling time (pulling out date)		N/A	May. 27th, 2021	Jun. 29th, 2021	Jul. 28th,2021	Oct. 26th,2021
Tests	Acceptance Criteria	Initial	1M	2M	3M	6M
Erucic Acid	NMT 250 µg/mL.	ND	<64 µg/mL (23 µg/mL)[5]	<64 µg/mL (46 µg/mL)	<64 µg/mL (63 µg/mL)	88 µg/mL

Defendants Concede Their Erucic Acid Specification Applies to Accelerated Conditions

64:22 Q. If you go to Page 8, which has Bates No.
64:23 ending in 34700 at bottom right corner, do you see
64:24 a row for "erucic acid"?
64:25 A. Yes.
65:01 Q. And the acceptance criteria here states
65:02 for release it's no more than 100 mg/ml, and for
65:03 stability, it's no more than 250 mg/ml.
65:04 Do you see that?
65:05 A. Yes.
65:06 Q. And you testified earlier that stability
65:07 is the same as shelf-life specification, correct?
65:08 A. Yes.
65:09 Q. Let's go to Page 18 ending in Bates
65:10 No. eVenus-00034790.
65:11 Do you see Table 3.2.P.5.6.13, Test
65:12 Results for Erucic Acid and LEPC?
65:13 A. Table 13?
65:14 Q. Table 3.2.P.5.6.13, yes.
65:15 A. Yes.

65:16 Q. Do you see the accelerated six-month data
65:17 for erucic acid listed in this table for both the
65:18 proposed generic drug and RLD?
65:19 A. Yes.
65:20 Q. And RLD refers to Exparel, right?
65:21 A. Yes.
65:22 Q. Does the stability acceptance criteria
65:23 apply here to the accelerated six-month data?
65:24 A. Yes.

Dr. Hongying Cui
Project Manager at
Jiangsu Hengrui
JTX-4285 at 64:22-65:24

The Erucic Acid Specification Applies to Accelerated Conditions

Q. Do you see any conditions, such as temperature or time, included in the shelf life specification?

A. No. The shelf life specifications applies to all the temperatures, all the conditions, and all the time points.

Q. Did defendants use the shelf life specification to test erucic acid under accelerated conditions?

A. Yes.

Dr. Sami Karaborni

Tr. at 277:20-23; 279:14-16

Defendants' Excuse

The shelf-life specification for the commercial ANDA Products does not address the issue of infringement. The shelf-life testing that will apply for the commercial ANDA Products, once approved by the FDA, is conducted at 5 °C, not at 25 °C. RFOF 42-46. There is no requirement for testing at 25 °C for the ANDA Products once approved by the FDA, or any particular concentration of erucic acid

and allows infringement. Rather, the ANDA is silent on the erucic acid concentration after storage at 25 °C and hence reliance on the logic of *Sunovion* would be legal error. No matter what the concentration of erucic acid after storage

The Federal Circuit's *Glaxo* and *Ferring* cases make clear that when an ANDA does not contain a specification that speaks directly to whether the commercial products, once approved by the FDA, will meet a particular claim limitation, the court must look to actual batch data to determine whether the commercial product, as sold, is likely to infringe. Under this controlling law, Pacira has not proven infringement.

Defendants' Post-Trial Br. on Non-Inf. at 3, 10, 19

PACIRA

Defendants' Batch Data

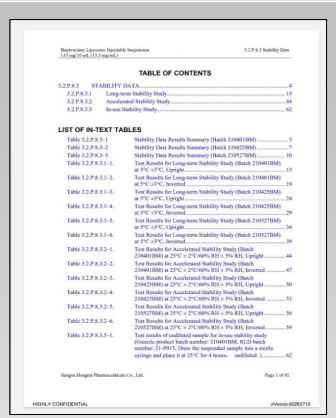


TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

JTX-4029 (10mL 3.2.P.8.3 Stability Data)

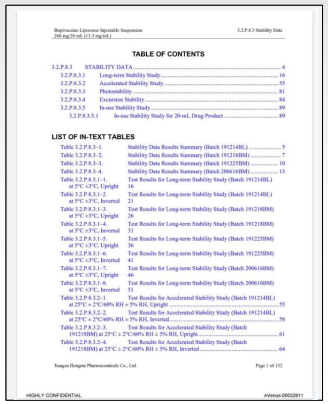


TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

JTX-4021 (20mL 3.2.P.8.3 Stability Data)

ANDA Batch No.	Erucic Acid (µg/mL) at 25°C after one month	
	Upright	Inverted
191214BL (20mL)	Not Detected	Not Detected
191218BL (20mL)	Not Detected	Not Detected
191225BM (20mL)	Not Detected	Not Detected
200616BM (20mL)	<64* (40)	<64* (37)
210401BM (10mL)	<64* (31)	<64* (38)
210425BM (10mL)	<64* (23)	<64* (24)
210527BM (10mL)	<64* (37)	<64* (35)

ANDA Batch No.	Erucic Acid (µg/mL) at 25°C after six months	
	Upright	Inverted
191214BL (20mL)	123	120
191218BL (20mL)	118	116
191225BM (20mL)	118	120
200616BM (20mL)	139	134
210401BM (10mL)	101	96
210425BM (10mL)	88	83
210527BM (10mL)	123	126

*64 µg/mL is the LOQ of erucic acid

Sunovion Applies Unless the ANDA is Silent

"[I]f a **product** that an **ANDA applicant is asking the FDA to approve** for sale falls within the scope of an issued patent, a judgment of infringement must necessarily ensue."

-*Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013)

"Even where internal documents suggest that a generic product will not meet a claim limitation in practice, **representations about the ANDA's scope control the infringement analysis**."

"**When an ANDA is silent** with respect to a claim limitation, ***Sunovion* does not govern**[.]"

-*Par Pharm., Inc. v. Hospira, Inc.*, 835 F. App'x 578, 585-86 (Fed. Cir. 2020) (emphasis added)

Defendants' ANDA is Not Silent

- Defendants conducted accelerated stability testing on all seven ANDA batches.
- The criteria Defendants applied – NMT 250 µg/mL erucic acid – encompasses the contested claim limitations.
- Defendants relied on this stability data in their ANDA.

Defendants Concede Accelerated Stability Testing is Required by FDA

Q. Dr. Schwendeman, you agree that the accelerated stability data at 25 degree Celsius for six months is required for defendants' ANDA?

A. Yes. I do agree with that, yes.

Dr. Anna Schwendeman
trial transcript at
502:10-13

ANDA Must Be Silent to Resort to Batch Data to Attempt to Demonstrate Non-Infringement

ANDA Silent	ANDA Not Silent
Ferring I	*Sunovion*
Medicines	*Par*
Glaxo	*Exela*
Ferring II Pre-amendment	*Ferring II* Post-amendment

Like the ANDA in *Par*, Defendants' ANDA Speaks to Infringement

- Patent claim to "about 0.01 to 0.4 mg/mL of a transition metal complexing agent." *Par Pharm.*, 835 F. App'x at 580.

- ANDA did not even address amounts of "transition metal complexing agent." *Id.* at 582, 586.
  - ANDA included statement of compliance with ICH Guidelines for "transition metal impurities" – up to 30% of the permitted daily exposure. *Id.* at 586.
  - Compliance with ICH Guidelines was required by FDA. *Id.*
  - Post-approval "[d]rug product testing is not required" for elemental impurities. *Id. at* 582.

- Par's expert used upper limit of ICH Guidelines for impurities (up to 30%) to calculate how much transition metal complexing agent the ***ANDA would permit***. *Id.*
- Hospira's expert used the ***measured amounts*** of transition metals in the ANDA batches. *Id.*

Sunovion Applies Regardless of Post-Approval Testing Commitment

- "Regarding the transition metal complexing agent claim limitation, the evidence showed that Hospira's ANDA specifies a particular concentration of citric acid, a known chelating agent, and also states that the ANDA product's 'elemental impurities' (which include transition metals, as noted *supra*) satisfy the requirements of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Humane Use (ICH) Q3D guidelines. The referred-to ICH Q3D guidelines specify that (to avoid the need for additional controls) elemental impurities in drug products be less than 30% of the specified permitted daily exposure (PDE). ***In the table it presented to the FDA, Hospira represented that '[d]rug product testing is not required' because "[e]lemental impurity levels for potential elements tested were found to be consistently less than 30% of the ... PDE."***"
  - *Par*, 835 F. App'x at 582 (citations omitted).

Like the ANDA in *Par*, Defendants' ANDA Speaks to Infringement

"Here, we conclude, *Sunovion* governs." *Id.* at 586.

"The ***ANDA states*** in a line entry in a table that ***its product satisfies the ICH Q3D guidelines***, ***meaning that it can market and sell a product with up to 30%*** of the permitted daily exposure of transition metal impurities. . . . ***Thus, unlike in Ferring,*** the ***ANDA is not silent*** as to whether Hospira's product ***could contain sufficient concentrations*** of elemental impurities such that citric acid would complex with the transition metals in a high enough concentration ***to satisfy the limitation*** requiring 'about 0.01 to 0.4 mg/mL of a transition metal complexing agent.'" **Sunovion *therefore applies***." *Id.* (cleaned up) (emphasis added).

Defendants' Incorrect Application of *Ferring I*

are those that will apply to the commercial products, once approved by the FDA. In other words, the question for infringement does not hinge on the criteria that were used as the basis for analytical comparisons during development, but instead on what specification will apply to the product as sold after approval by the FDA.[7] *Ferring I*, 764 F.3d at 1409 ("The infringement evaluation is concerned only with the final, coated commercial tranexamic acid tablets for which Watson sought and was granted FDA approval to market as a generic version of a treatment of menorrhagia."). Pacira's argument boils down to an assertion that infringement can

The ANDA in *Ferring I* was Silent on Infringement

- Claim required **less than about 70%** dissolution **at 45 minutes**. 764 F.3d 1401, 1403 (Fed. Cir. 2014).
- ANDA had **no specification on dissolution** of the **final coated tablets** for which the ANDA was seeking approval.
- To show infringement, patentee tried to rely on **non-ANDA documents** related to applicant's internal testing of **experimental, uncoated product**. *Id.* at 1405.
- Federal Circuit rejected reliance on testing because "it does not provide any data for the dissolution release rate of tranexamic acid from Watson's **finished, coated commercial tablets**." *Id.* at 1410.

➢ In contrast, Defendants here applied their specification of NMT 250 µg/mL to accelerated testing of **the 7 ANDA batches – i.e., Defendants' proposed commercial product**.

The ANDA in *Ferring II* was Amended to Avoid Infringement

- Claim required **less than about 70%** dissolution **at 45 minutes**. 764 F.3d 1382, 1387 (Fed. Cir. 2014).
- In *Ferring II*, the ANDA originally specified ***not*** less than 80% dissolution **at 60 minutes**.
  - Original ANDA therefore silent.
- ANDA was later amended to specify ***not*** less than 75% dissolution at 45 minutes.
  - Amended ANDA therefore had an on-point specification that required non-infringement – i.e., no longer silent.

Defendants' ANDA Reaffirms Reliance on Erucic Acid Accelerated Stability Data

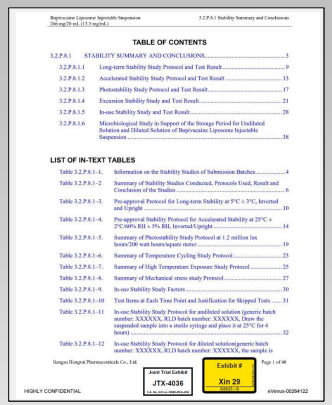


TABLE OF CONTENTS

3.2.P.8.1 STABILITY SUMMARY AND CONCLUSIONS 3

3.2.P.8.1.1 Long-term Stability Study Protocol and Test Result 9

3.2.P.8.1.2 Accelerated Stability Study Protocol and Test Result 13

3.2.P.8.1.3 Photostability Study Protocol and Test Result 17

3.2.P.8.1.4 Excursion Stability Study and Test Result 21

3.2.P.8.1.5 In-use Stability Study and Test Result 28

3.2.P.8.1.6 Microbiological Study in Support of the Storage Period for Undiluted Solution and Diluted Solution of Bupivacaine Liposome Injectable Suspension 36

LIST OF IN-TEXT TABLES

Table 3.2.P.8.1-1. Information on the Stability Studies of Submission Batches 4

Table 3.2.P.8.1-2. Summary of Stability Studies Conducted, Protocols Used, Result and Conclusion of the Studies 6

Table 3.2.P.8.1-3. Pre-approval Protocol for Long-term Stability at 5°C ± 3°C, Inverted and Upright 10

Table 3.2.P.8.1-4. Pre-approval Stability Protocol for Accelerated Stability at 25°C ± 2°C/60% RH ± 5% RH, Inverted/Upright 14

Table 3.2.P.8.1-5. Summary of Photostability Study Protocol at 1.2 million lux hours/200 watt hours/square meter 19

Table 3.2.P.8.1-6. Summary of Temperature Cycling Study Protocol 23

Table 3.2.P.8.1-7. Summary of High Temperature Exposure Study Protocol 25

Table 3.2.P.8.1-8. Summary of Mechanical stress study Protocol 27

Table 3.2.P.8.1-9. In-use Stability Study Factors 30

Table 3.2.P.8.1-10 Test Items at Each Time Point and Justification for Skipped Tests 31

Table 3.2.P.8.1-11 In-use Stability Study Protocol for undiluted solution (generic batch number: XXXXXX, RLD batch number: XXXXXX, Draw the suspended sample into a sterile syringe and place it at 25°C for 4 hours) 32

Table 3.2.P.8.1-12 In-use Stability Study Protocol for diluted solution(generic batch number: XXXXXX, RLD batch number: XXXXXX, the sample is

Hanguo Hongrui Pharmaceuticals Co., Ltd. Page 1 of 48

Joint Trial Exhibit JTX-4036

Exhibit # Xin 29

HIGHLY CONFIDENTIAL eVenus-00264122

JTX-4036 (20mL 3.2.P.8.1 Stability Summary) at JTX-4036..0004, -.0006

For the photostability study, excursion stability study, and in-use stability study (fresh samples) have been completed before the method change of cholesterol, thus only cholesterol was investigated during the photostability study, excursion stability study, and in-use stability study, and the test results showed no significant change. Considering that LEPC and erucic acid could reflect the degradation of four lipids (see 3.2.P.5.5.1 for the justification), the results of LEPC and erucic acid during these studies had no significant change and met the proposed acceptance criteria, we can predict that no obvious degradation of lipids would be observed. Thus, there are no risk concerns stemming from the degradation of lipids.

The 6 months accelerated stability data showed that pH of this product had the tendency to decrease, the results of content of erucic acid, LEPC, in vitro release and particle size distribution had the tendency to increase, and the results met the acceptance criteria. The impurity

Claim 7 is Valid

Defendants' Try To Meet Their Clear and Convincing Evidence Burden with the Same Prior Art that was Before the Examiner

- "As stated, the first paragraph of § 282 provides that '[a] patent shall be presumed valid' and '[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.'" *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 100 (2011).
- The party challenging validity must demonstrate invalidity by clear and convincing evidence. *Id.* at 95.
- "A party challenging validity shoulders an enhanced burden if the invalidity argument relies on the same prior art considered during examination by the U.S. Patent and Trademark Office." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011).

Claim 7 is Not Obvious

Defendants Rely on the Prior Art EXPAREL® that the Inventors Were Trying to Improve

Range of Six Month Erucic Data: 110–127 µg/mL

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C) of 45 L Commercial Exparel before 1/22/21

Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
					0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
14-4012	45L	Suite C (Skid 100)	10/29/2014	25	ND	27	36	61	123	6.1	Y	JTX-4049.0025
14-4013	45L	Suite C (Skid 100)	10/31/2014	25	ND	LT20	36	58	113	6.1	Y	JTX-4049.0026
14-4015	45L	Suite C (Skid 100)	11/5/2014	25	ND	LT20	36	58	114	6.4	Y	JTX-4049.0027
14-P004	45L	Suite C (Skid 200)	12/1/2014	25	ND	LT20	43	53	118	6.4	Y	JTX-4049.0028
16-3088	45L	Suite C (Skid 200)	6/8/2016	25	ND	25	35	53	110	6.5	Y	JTX-4049.0033
16-3089	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	34	54	111	6.5	Y	JTX-4049.0032
16-3090	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	36	54	114	6.5	Y	JTX-4049.0034
18-P009	45L	Suite C (Skid 100 and 200)	6/4/2020 2018	25	LT20	28	42	58	116	6.5	Y	JTX-4049.0051 DTX-2512.23
18-P004	45L	Suite C (Skid 100 and 200)	6/5/2020 2018	25	LT20	28	40	56	111	6.5	Y	JTX-4049.0052 DTX-2512.23
18-P063	45L	Suite C (Skid 100)	10/29/2020 2018	25	LT20	28	48	62	127	6.5	Y	JTX-4049.0053

DTX-3111

HIGHLY CONFIDENTIAL

DTX-3111.1

DTX-3111

Validity FOFCOLs ¶¶ 196-197, 252

PACIRA

Defendants Must Prove Motivation to Modify and a Reasonable Expectation of Success

- A party asserting that a patent claim is obvious must show "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Novartis Pharm. Corp. v. West-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir. 2019).

- For single reference obviousness, "there must be a showing of a suggestion or motivation to modify the teachings of that reference to the claimed invention in order to support the obviousness conclusion." *SIBIA Neuroscis., Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000).

Hindsight Is Not Permitted

- Obviousness is evaluated at the time of the invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

- "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *Id.*

Defendants Must Address Objective Indicia

- Objective indicia "also serve to guard against slipping into use of hindsight, and resist the temptation to read into the prior art the teachings of the invention at issue." *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (quotation omitted).

- The Federal Circuit "has emphasized that consideration of the objective indicia is part of the whole obviousness analysis, not just an afterthought." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013).

Dr. Schwendeman Did Not Opine on Motivation to Modify and Reasonable Expectation of Success

Dr. Anna Schwendeman
trial transcript at

Defendants Ignore: Based on its Prior Experience with EXPAREL® Scale-up, Pacira Doubted 200-L Could be Done

Q. Why is it that Pacira would pursue a radically different technology if it had already scaled up once from 25 to 45-liter?

A. It was that original scale-up and the issues we ran into that gave us kind of pause that scaling up from 45 to any scale greater than that would either cause too long of a timeline or it would never be able to be achieved. It's never been done before.

Q. And how high up in the company did this skepticism go as far -- did this skepticism go as far as you were aware?

A. Yeah. I mean, people were taking bets and one of the betters was a senior board member who had doubt that the 200-liter would ever be able to produce anything.

Jeff Hall
trial transcript at
95:23-96:10

Defendants Ignore: Pacira Worked On "Radically Different" Scale-Up Approaches in Parallel

2005
Joined Pacira

2008
Joined Pacira

45L

45L

Team 200L

Team Spray

2012
Commercial launch – 45L

2013
2 new 45L skids

2017
Pacira gives up on spray

PACIRA BIOSCIENCES, INC.

2020
sNDA submitted

2021
'495 filed

2021
sNDA Approved & Patent Issued

2005 2010 2015 2020 2025

Validity FOFCOLs ¶¶ 113-118

PACIRA

Defendants Ignore: Pacira Faced Numerous Obstacles Scaling Up EXPAREL® - "Five years of trial and error"

Q. Can you quantify how big of a struggle this was?

A. Yeah. So in order to get the skid to produce material that we could sell, or at least seek approval from the FDA, it required upwards -- more than 100 development batches.

Q. Were all those batches made after you arrived on scene?

A. Yeah. Yes.

Q. So after 2017?

A. Yes.

Q. So five years, over 100 batches; is that right?

A. That's right.

Q. Do you have an understanding of how much money was invested in that project?

A. All told, over $100 million.

Q. In your view and experience, what do those 100-plus batches represent?

A. Five years of trial and error.

Jeff Hall
trial transcript at
100:10-25

Defendants Ignore: Literature Reports the Problem with Liposomes is Instability

Liposomal Drug Product Development and Quality: Current US Experience and Perspective

Mamta Kapoor,[1] S

Product Stability

Liposomes are thermodynamically unstable and therefore are prone to physical instabilities such as fusion or aggregation during storage (2). Lipid molecules are also prone to chemical instabilities such as hydrolysis (forming lysolipids) and oxidative degradation during storage. Stability and post-approval stability protocols are another developmental area that should be understood for liposomal formulations. Often, these protocols include testing of physical and chemical stability of liposomal products in terms of particle size, lipid degradants (lysolipids and fatty acid content), phase transition temperature, etc. (5) in order to assure high product quality during storage.

JTX-4210.0008

Kapoor et al. (2017)

Defendants Ignore: MVL manufacturing is a "Marathon Task"

A review on multivesicular liposomes for pharmaceutical applications: preparation, characterization, and translational challenges

Akash Chaurasiya[1] · Amruta Gorajiya[2] · Kanan Panchal[1] · Sumeet Katke[1] · Ajeet Kumar Singh[3]

Methods of MVL preparation

Large-scale manufacturing of MVL is a complex and marathon task due to the unique characteristic of this dosage form and critical unit operations. Proper understanding of the mechanism of particle formation, the rationale for using each composite, and effective and efficient use of equipment/techniques are essential. The double emulsification method is proven to successfully translate MVL from laboratory to commercial manufacturing [22].

JTX-4230.0004

Chaurasiya et al. (2021)

Defendants Ignore: FDA States that Liposomes are Complex and Sensitive Formulations

- FDA Guidance on Liposome Drug Products (2018):

> Liposome drug products are sensitive to changes in the manufacturing conditions, including changes in scale (size of the batches). Appropriate process controls should be established during product development. Prior knowledge can be leveraged and risk assessment techniques can be used to identify manufacturing process parameters that potentially affect finished product quality.

> Liposome drug products are complex and sensitive formulations and response to CMC changes is less predictable than with more conventional formulations. Therefore, changes to the formulation, container closure, site of manufacture, or manufacturing process (including substantive equipment and scale changes) will usually require a prior approval supplement. In vivo studies may be needed to assess changes that can affect the performance of the drug product. You can contact the appropriate review division[16] associated with your application if you have questions regarding the type of information to generate or the appropriate reporting mechanism for a postapproval change.[17]


Liposome Drug Products

Guidance for Industry

PTX-362,-.0008, -.0013

Defendants Ignore: Dr. Schwendeman's Opinions Outside This Litigation

Q. Now, there are a lot of reasons why Exparel is so complicated, right?

A. Yeah. It is complicated -- complicated product to manufacture, complicated product to characterize.

Q. And you talk about some of those reasons in your paper, right?

A. I do, yes.

Dr. Anna Schwendeman
trial transcript at
479:13-19

Exparel is a bupivacaine multivesicular liposomes (MVLs) formulation developed based on the DepoFoam technology. The complex composition and the unique structure of MVLs pose challenges to the development and assessment of generic versions. In the present work, we developed a panel of analytical methods to characterize


International Journal of Pharmaceutics

Characterization of exparel bupivacaine multivesicular liposomes

PTX-425

PAC-EXPAREL04163987

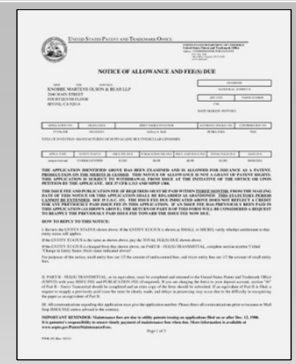
PTX-425

Defendants Ignore: The Examiner Already Considered and Rejected Defendants' Obviousness Argument

8. The following is an examiner's statement of reasons for allowance: The declaration of Ms. Los attests that the method claims as amended are not obvious in view of the teachings of Camu in view of Li. The prior art fails to teach the claimed degradation product of erucic acid after 6 months storage at 25C. Furthermore the combined art does not teach the claimed concentration of bupivacaine. The Office finds the declaration persuasive that the combined prior art does not teach the claimed method of preparation of MVL having the claimed storage stability.

Q. Now, what you didn't say in this paragraph or elsewhere is what the examiner said in that notice of allowance, right?

A. Yes, I did not say.



JTX-4001.2311

(Statement of Reasons for Allowance)

Dr. Anna Schwendeman

Trial Tr. at 538:15-17

Dr. Klibanov's Opinion on No Reasonable Expectation of Success Is Unrebutted

- Defendants presented no evidence of motivation to modify prior art EXPAREL® to achieve claim 7 or a reasonable expectation of success.

> Do you have an opinion on reasonable expectation of success at the time of the invention?
>
> A. I do. In my opinion, a person of ordinary skill in the art would have no reason to have reasonable expectation of success because if -- because it was unexpected that it would be possible to scale up the process for the production of bupivacaine MVL and still achieve even the same stability, much less improved stability as is claimed in Claim 7 of the '495 patent.

Dr. Alexander Klibanov
trial transcript at
720:14-22

The Unrebutted Objective Indicia Support Non-Obviousness

- A showing of unexpected results, i.e. a showing that "the claimed invention exhibits some superior property or advantage that a person in the relevant art would have found surprising or unexpected" supports a finding of nonobviousness because "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

- "The existence of a long-felt but unsolved need that is met by the claimed invention is further objective evidence of non-obviousness." *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017).

Dr. Schwendeman Did Not Analyze Whether Improved Stability of the Invention Was Expected Compared to the Asserted Prior Art

Q. Dr. Schwendeman, in your opinion, is the stability measured by concentration of erucic acid at one and six months of the 200-liter batches unexpectedly better than the 45-liter batches?

A. I do not think so. I think there is a very large range for 45-liter from 78 to 146. If you put all the 200-liter data, there is a very large range as well from -- some are 92 to 133. There is no difference. They created two overlapping ranges. They have the same stability at six months at 25 degrees.

Dr. Anna Schwendeman
trial transcript at
462:11-20

Dr. Schwendeman Impermissibly Relied on Non-Prior Art

Q. Now, Dr. Schwendeman, you understand that in the obviousness analysis, you are not permitted to assume that a person of skill would know about batches that are not prior art?

A. Yes, correct.

Dr. Anna Schwendeman
trial transcript at
536:18-22

"Unexpected results are shown in comparison to what was known, not what was unknown." *Millenium Pharms., Inc. v. Sandoz, Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017).

Unexpected Improved Stability

FIG. 3B is a line chart showing erucic acid concentration as a function of incubation time at 25° C. of the bupivacaine-MVL compositions prepared by the new process described herein as compared to those prepared by the existing commercial process. It was observed that the rate of lipid hydrolysis was 18% lower in the bupivacaine-MVL compositions prepared by the new process.

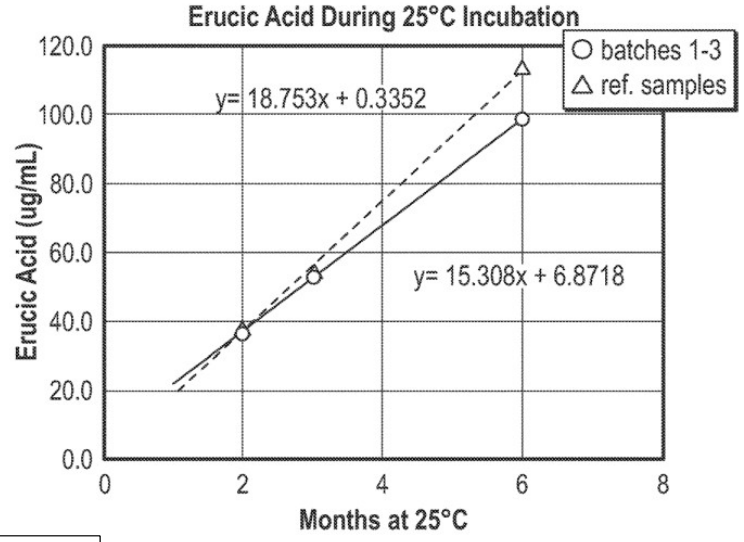


FIG. 3B

JTX-4121.0010
Col. 21:34-41

by the existing commercial process. The improved lipid stability (as indicated by the erucic acid concentration) observed in the bupivacaine MVLs prepared by the presently described process was surprisingly unexpected.

Dr. Klibanov's Opinion on Unexpected Results Was Unrebutted

Do you have an opinion on reasonable expectation of success at the time of the invention?

A. I do. In my opinion, a person of ordinary skill in the art would have no reason to have reasonable expectation of success because if -- because it was unexpected that it would be possible to scale up the process for the production of bupivacaine MVL and still achieve even the same stability, much less improved stability as is claimed in Claim 7 of the '495 patent.

Dr. Alexander Klibanov
trial transcript at
720:14-22; 722:10-15

Validity FOFCOLs ¶¶ 260-261, 269

PACIRA

Pacira Presented Unrebutted Evidence of Long-Felt Unmet Need

Q. Let's talk now about the other objective indicia you mentioned, long-felt, unmet need.

Do you have an opinion on that?

A. Yes. I believe that there was a long -- a long-felt, unmet need that was well acknowledged at the time of the invention and that the larger scale and most stable Exparel met -- met that long-felt need.

Q. Now, before we get into the details of your opinion, did Dr. Schwendeman mention long-felt, unmet need in her testimony?

A. She did not.

Dr. Alexander Klibanov
trial transcript at
726:11-727:23

Pacira Presented Unrebutted Evidence of Long-Felt Unmet Need

Q. And at Column 1, lines 32 through 36, does the '495 patent provide any additional information on long-felt, unmet need?

A. Yes. It specifically states that given the addictive nature of opioids, and the opioid epidemic, there is an urgent need for new and improved large scale productions of Exparel to meet the substantial and growing market demand.

Q. And in your opinion, Dr. Klibanov, did the larger-scale stable Exparel disclosed in the '495 patent satisfy that need?

A. Yes, it does. Obviously, much more of Exparel could be produced if you do it on a 200-liter scale than on a 45-liter scale.

Dr. Alexander Klibanov
trial transcript at
726:11-727:23

Defendants Propose that the Court Rely on Overlapping Range Case Law to Short Circuit the Obviousness Inquiry

In analyzing obviousness, "[i]f the relevant comparison between a disputed claim limitation and the prior art pertains to a range of overlapping values . . . . such an overlap creates a presumption of obviousness, and . . . the burden of production falls upon the patentee to come forward with pertinent evidence that the overlapping range would not have been obvious in light of the prior art." *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1341 (Fed. Cir. 2020) (citing *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006-08 (Fed. Cir. 2018) (collecting cases)). This presumption also exists where the ranges do not overlap but "are so close that *prima facie* one skilled in the art would have expected them to have the same properties." *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985); *accord In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003).

Validity FOFCOLs ¶ 612; Defs. Br. at 36

PACIRA

Prima Facie Obviousness Does Not Apply Solely Because Claimed Ranges Approach, But Do Not Overlap

- "While the court in *In re Peterson* cited the proposition from *Titanium Metals* that 'a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties,' *id.* at 1329 (citing *Titanium Metals*, 778 F.2d at 783) (emphasis omitted), that statement was dicta; all of the ranges in *In re Peterson* overlapped at least to some degree." *In re Patel*, 566 F. App'x 1005, 1010 (Fed. Cir. 2014).

- "We find that the PTAB erred in finding that the examiner established a prima facie case of obviousness *solely* because the claimed range and the prior art range approach one another." *Id.* at 1010.

In Defendants' Only Non-Overlapping Case (*Ortho-McNeil*), the Patentee Admitted There Was No Difference and No Unexpected Results

- Defendants only cite one case where (like here) the ranges did not overlap. *Ortho-McNeil Pharm. v. Teva Pharm. Indus., Ltd.*, 344 F. App'x 595 (Fed. Cir. 2009).

- *Ortho-McNeil* predates *In re Patel*.

- "Ortho-McNeil's problem, however, is that its own evidence indicates ***no perceptible difference*** in synergy between a weight ratio of 1:7.1 and 1:10—and indeed over a much broader range of ratios. ***Ortho–McNeil does not dispute this.***" *Id.* at 600 (emphasis added).

Pacira Presented Unrebutted Evidence of Difference in Kind

Q. Now, in light of these differences we've just discussed, are the erucic acid levels in prior art Exparel close to the levels in Claim 7?

A. I don't think that a person of ordinary skill in the art would find them close.

Q. And are these a difference in kind or a difference in degree?

A. They're difference in kind because what we have here is a new product, larger-scale product produced by a new process whereby this new product exhibits important new properties that I already talked about. So, to me and to a POSA, it's a difference in kind.

Dr. Alexander Klibanov
trial transcript at
715:1-12

Unrebutted Evidence that Improved Stability Was ***Not*** Expected

- Liposomes, and MVLs specifically, were known in the art to face challenges with stability.
  - Including FDA Guidance
- Inventors' own experience was that erucic acid levels were sensitive to manufacturing changes.
- Lower erucic acid over time was unexpected, particularly considering the challenges of scaling up.

The Only Person Who Asserts the Claims are Obvious is Funded by FDA to Help Develop Generic EXPAREL®

"Claim 7 is Obvious"

Dr. Anna Schwendeman

Q. And you receive money from the FDA to help get generic drugs on the market, right?

A. I receive money from the FDA. It's a open competition.

* * *

Q. Dr. Schwendeman, you did all this work to help with the development of generic versions of Exparel, right?

A. Correct.

Tr. at 475:23-25; 481:19-21

"Claim 7 is Not Obvious"

Dr. John Grigsby

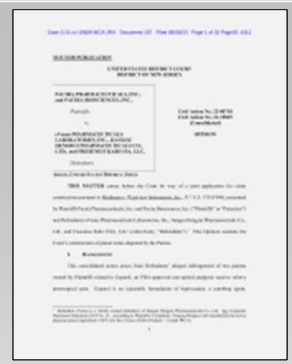
Dr. Alexander Klibanov

Primary Patent Examiner

Defendants Failed to Address An Entire Limitation in Claim 7

In the Court's *Markman* Order, "Prepared By A Commercial Scale Process" Connotes Specific Structure

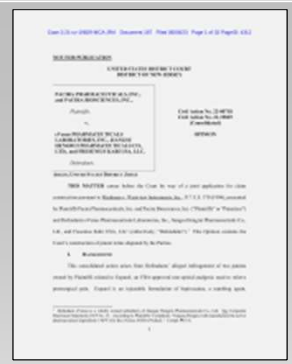
> Here, the Court agrees with Plaintiffs that the preamble is not a product-by-process limitation because it informs the structure and contains structural differences than the existing art. While the claim as a whole describes a process, intrinsic evidence demonstrates that the term connotes specific structure. The specification Patent at 4:26-40. More specifically, "the



ECF No. 187 at 19
(Claim Construction Opinion)

Under *Amgen*, Structure Imparted by a Process Must Be Considered for Invalidity

Here, the Court agrees with Plaintiffs that the preamble is not a product-by-process limitation because it informs the structure and contains structural differences than the existing art. While the claim as a whole describes a process, intrinsic evidence demonstrates that the term connotes specific structure. The specification Patent at 4:26-40. More specifically, "the



ECF No. 187 at 19
(Claim Construction Opinion)

"Those structural and functional differences are not explicitly part of the claim, yet are relevant as evidence of no anticipation because of the source limitation." *Amgen, Inc. v. Hoffman La-Roche, Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009).

Dr. Schwendeman Disagreed with the Court's *Markman* Order That Connotes Specific Structure

Here, the Court agrees with Plaintiffs that the preamble is not a product-by-process limitation because it informs the structure and contains structural differences than the existing art. While the claim as a whole describes a process, intrinsic evidence demonstrates that the term connotes specific structure. The specification Patent at 4:26-40. More specifically, "the

Q. It's your position that the phrase "prepared by a commercial scale process" does not inform us of the structural differences of the commercial scale process of the '495 patent, true?

A. Not about structural differences. I believe both products were prepared by commercial process.

ECF No. 187 at 19
(Claim Construction Opinion)

Dr. Anna Schwendeman
Tr. at 510:11-15

Dr. Schwendeman's Opinion on "Prepared by a Commercial Scale Process"

Dr. Anna Schwendeman

Dr. Schwendeman Was Required, and Failed, to Opine on All Claim Limitations

- "[T]estimony concerning anticipation must be testimony from one skilled in the art and ***must identify each claim element***, state the witnesses' interpretation of the claim element, ***and explain in detail how each claim element is disclosed in the prior art reference***." *Schumer v. Lab. Comp. Sys., Inc.*, 308 F.3d 1304, 1315-16 (Fed. Cir. 2002) (emphasis added).

Claim 7 is Not Anticipated

Defendants Could Not Identify Any Prior Art Batch that Anticipates

Range of Six Month Erucic Data:
110–127 µg/mL

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C)
of 45 L Commercial Exparel before 1/22/21

Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
					0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
14-4012	45L	Suite C (Skid 100)	10/29/2014	25	ND	27	36	61	123	6.1	Y	JTX-4049.0025
14-4013	45L	Suite C (Skid 100)	10/31/2014	25	ND	LT20	36	58	113	6.1	Y	JTX-4049.0026
14-4015	45L	Suite C (Skid 100)	11/5/2014	25	ND	LT20	36	58	114	6.4	Y	JTX-4049.0027
14-P004	45L	Suite C (Skid 200)	12/1/2014	25	ND	LT20	43	53	118	6.4	Y	JTX-4049.0028
16-3088	45L	Suite C (Skid 200)	6/8/2016	25	ND	25	35	53	110	6.5	Y	JTX-4049.0033
16-3089	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	34	54	111	6.5	Y	JTX-4049.0032
16-3090	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	36	54	114	6.5	Y	JTX-4049.0034
18-P009	45L	Suite C (Skid 100 and 200)	6/4/2020 2018	25	LT20	28	42	58	116	6.5	Y	JTX-4049.0051 DTX-2512.23
18-P004	45L	Suite C (Skid 100 and 200)	6/5/2020 2018	25	LT20	28	40	56	111	6.5	Y	JTX-4049.0052 DTX-2512.23
18-P063	45L	Suite C (Skid 100)	10/29/2020 2018	25	LT20	28	48	62	127	6.5	Y	JTX-4049.0053

DTX-3111

HIGHLY CONFIDENTIAL

DTX-3111.1

DTX-3111

Defendants Rely Exclusively on ***NON***-Prior Art

Opening Invalidity Report

Batch	Erucic acid after storage at 25° C for one month (µg/mL)	Erucic acid after storage at 25° C for six months (µg/mL)	Bates Citation
13-2205 (Registration)	Less than 20	91	PAC-EXPAREL00348728 at -729 PAC-EXPAREL00355009 at -009, -011
13-2206 (Registration)	Less than 20	92	PAC-EXPAREL00348269 at -270
18-SS-020 (PPQ)	Less than 20	98	PAC-EXPAREL02782182 at -182, -184
18-SS-021 (PPQ)	Less than 20	99	PAC-EXPAREL02998519 at -519, -520
18-SS-022 (PPQ)	Less than 20	93	PAC-EXPAREL02677008 at -008, - 010
18-SS-024 (PPQ)	Less than 20	100	PAC-EXPAREL02782716 at -716, -718
037188 (Registration, Stability)	23	90	PAC-EXPAREL03987429 at -431
037190 (Registration, Stability)	Less than 20	83	PAC-EXPAREL03987429 at -435
037191 (Registration, Stability)	ND	80	PAC-EXPAREL03987429 at -437
037192 (Registration, Stability)	ND	80	PAC-EXPAREL03987429 at -439
037193 (Registration, Stability)	ND	78	PAC-EXPAREL03987429 at -441

Batch	Erucic acid after storage at 25° C for one month (µg/mL)	Erucic acid after storage at 25° C for six months (µg/mL)	Bates Citation
13-2204 (Registration)	ND	93	PAC-EXPAREL00348325 at -326 PAC-EXPAREL00355009 at -009, -011 PAC-EXPAREL02551523 at -524, -585

Batch	Erucic acid after storage at 25° C for one month (µg/mL)	Erucic acid after storage at 25° C for six months (µg/mL)	Bates Citation
126837 (Bioequivalence)	Less than 20	102	PAC-EXPAREL03987429 at -445

2023-08-10 eVenus Opening Invalidity Rpt of Schwendeman at ¶179

PDX-7.3

PACIRA

PTX-492

Defendants' Excuses For Relying on ***NON***-Prior Art

- Defendants assert that non-prior art can prove the properties of prior art
- Pacira referred to non-prior art as "representative" of and "equivalent" to commercial product
- Defendants argue that it is likely a prior art batch had the claimed erucic acid levels

The *Exela* Court Rejected Defendants' Exact Argument Here

- In *Exela*, the court rejected the argument that a certificate of analysis for a non-prior art lot proved that the drug product "that was publicly sold from 2003 to 2016" met a claim limitation for aluminum levels. 620 F. Supp. 3d 108, 129-30 (D. Del. 2022).
- The defendant "offered no evidence that the lot tested in the Sandoz Canada certificate was ever sold" and that "[n]o testimonial or documentary evidence supports that the lot tested in the [] certificate was ever in the prior art." *Id.*
- "[T]he Court cannot extrapolate from one Certificate of Analysis that there must have been at least one commercial batch that met the limitation." *Id.* at n.11.

The Exela Court Rejected Defendants' Exact Argument Here

- "There is, however, insufficient evidence that the Sandoz Canada certificate describes a lot that was in public use, on sale, or otherwise available to the public in the United States (or elsewhere)" *Id.* at 141.
- Defendants' attempt to distinguish *Exela* by asserting that there are "numerous batches" here.
- But Defendants fail to address the *Exela* court's reasoning on ***why*** the CoA could not be used to predict the properties of unidentified prior art batches: variability.

➢ "As Dr. Baertschi agreed, the aluminum levels in the Sandoz product "varied quite a bit." *Id.* at n.11.

➢ Dr. Schwendeman agrees: "You can't look at a sample and predict the results . . . . [y]ou have to run the test[.]" Tr. 487:1-5.

Defendants' Cited Cases Are All About Predictable Machines and Processes, Unlike the "Huge" Variability Here

- *Sonoscan, Inc. v. Sonotek, Inc.*, was about a microscope with the same model number. 936 F.3d 1261, 1263-64 (Fed. Cir. 1991).

- *Shuffle Tech Int'l, LLC v. Sci. Games Corp.*, was about photographs of a specific card shuffling machine. 2018 WL 2009504, at *4 (N.D. Ill. Apr. 29, 2018).

- *Unitherm Food Sys., Inc. v. Swift-Eckrich, Inc.*, was about video evidence of a process for browning precooked deli meat. 375 F.3d 1341, 1352-54 (Fed. Cir. 2004), *rev'd*, 546 U.S. 394 (2006).
  - *Unitherm* was also overturned by the U.S. Supreme Court, which Defendants notably failed to mention in their opening brief and failed to address in their reply brief ***even after*** Pacira pointed this out in its response.

Defendants Ask the Court to Find Inherency, but Avoid Saying "Inherency" to Short Circuit Their Burden

- "To establish that a prior art reference inherently—rather than expressly—discloses a claim limitation, ***the limitation at issue necessarily must be present,*** or [is] the natural result of the combination of ***elements explicitly disclosed by the prior art…Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.***" *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1391 (Fed. Cir. 2018) (emphasis added).

- *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995) (affirming finding "that Novopharm ***had not carried its burden*** of proving by clear and convincing evidence that practice of Example 32 of the '658 patent ***always produced*** Form 2 ranitidine hydrochloride, so that Form 2 was ***not inherently disclosed*** by Example 32").

Defendants' Excuses For Relying on ***NON***-Prior Art

- Defendants assert that non-prior art can prove the properties of prior art
- Pacira referred to non-prior art as "representative" of and "equivalent" to commercial product
- Defendants argue that it is likely a prior art batch had the claimed erucic acid levels

Undisputed: Representative Means Within Specification

3. Selection of Batches (2.1.3)

Data from formal stability studies should be provided on at least three primary batches of the drug substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as production batches and using a method of manufacture and procedure that simulates the final process to be used for production batches. The overall quality of the batches of drug substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale.

3. Selection of Batches (2.2.3)

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.


Guidance for Industry
Q1A(R2) Stability Testing of New Drug Substances and Products

JTX-4044.0006, -.0011

Undisputed: Equivalent Means Within Specification

For this, as well as for other reasons, *equivalent* does not necessarily mean *identical*. Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

1. Conformance to Specifications

An assessment of the effects of a change on the identity, strength, quality, purity, and potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected by the change conform to the approved specifications.[8] A *specification* is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. *Acceptance criteria* are numerical limits, ranges, or other criteria for the tests described (§ 314.3(b)). Conformance to a specification means that the


Guidance for Industry

Changes to an Approved NDA or ANDA

PTX-416.0011, -0009
(FDA Changes Guidance)

Dr. Schwendeman Agrees that the Different Standards at FDA and the PTO Are Like "Apples and Oranges"

Q. You agree --

A. I agree.

Q. -- that the difference between the equivalence and comparability standard with the FDA and the anticipation standard at the PTO are like apples and oranges to you, right?

A. To some degree the standards and the data that goes by, they see. FDA see all the data. USPTO clearly saw a subset of the data. But I do agree they look at them through blue or red glasses.

Q. Dr. Schwendeman, those standards are like apples and oranges to you?

A. Yes. Like apples and oranges, yes. Correct.

Dr. Anna Schwendeman
trial transcript at
505:22-506:8

Defendants' Excuses For Relying on ***NON***-Prior Art

- Defendants assert that non-prior art can prove the properties of prior art
- Pacira referred to non-prior art as "representative" of and "equivalent" to commercial product
- Defendants argue that it is likely a prior art batch had the claimed erucic acid levels

Dr. Schwendeman Admitted She Presented No Statistical Analysis for Her "Courtroom Full of Vials" Theory

Q. Instead, what you told the Court was that, given that there was a courtroom full of vials, that some of them must have had erucic acid level that you were looking for, 99 or less, right?

A. Yes. I strongly believe that, yes.

Q. Dr. Schwendeman, you didn't -- the Court didn't hear any statistical analysis in your direct examination, did it?

A. It didn't.

Q. You did not do -- I'm sorry. The Court did not hear any probability analysis to support your opinion, either, did it?

A. That is true.

Dr. Anna Schwendeman
trial transcript at
530:19-531:4

Dr. Schwendeman Believes It's Just a "Coincidence" That ***All Eleven*** Prior Art Batches Do Not Anticipate

Q. Do you believe, Dr. Schwendeman, it's just a coincidence that all 11 commercial batches measured at six months were at 110 or above?

A. I believe it's statistically absolutely possible because it's only 0.3 percent of all of the batches that are made. So if you take a good sample, I don't know, 10 percent, you would get to the range.

Dr. Anna Schwendeman
trial transcript at
530:12-18

Defendants' Excuses For Relying on ***NON***-Prior Art

- Defendants assert that non-prior art can prove the properties of prior art
- Pacira referred to non-prior art as "representative" of and "equivalent" to commercial product
- Defendants argue that it is likely a prior art batch had the claimed erucic acid levels

Defendants Tested Prior Art EXPAREL®

Q. Did Jiangsu Hengrui obtain samples of Exparel before 2021?

A. Yes.

Q. Did Jiangsu Hengrui perform testing on samples of Exparel before 2021?

A. Yes.

Dr. Hongying Cui

Project Manager at Jiangsu Hengrui

JTX-4285 at 147:16-21

Defendants' Results from Testing Prior Art EXPAREL®

"The Court Will Never Know" is ***Not*** Clear and Convincing Evidence

Q. So you agree that for the 45-liter Exparel batches that were sold, we'll never know if they meet the limitations of Claim 7, right?

A. Yeah. We could not go back and test and put every batch on stability at six months and then test all of them. That was not done, so --

Q. So the Court will never know, right?

A. Yes.

Dr. Anna Schwendeman
trial transcript at
532:20-534:15

Prior Art EXPAREL® Does Not Anticipate

Range of Six Month Erucic Data: 110–127 µg/mL

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C) of 45 L Commercial Exparel before 1/22/21

Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL) 0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	pH (external) 6 mo.	Commercially Sold	Exhibit #(s)
14-4012	45L	Suite C (Skid 100)	10/29/2014	25	ND	27	36	61	123	6.1	Y	JTX-4049.0025
14-4013	45L	Suite C (Skid 100)	10/31/2014	25	ND	LT20	36	58	113	6.1	Y	JTX-4049.0026
14-4015	45L	Suite C (Skid 100)	11/5/2014	25	ND	LT20	36	58	114	6.4	Y	JTX-4049.0027
14-P004	45L	Suite C (Skid 200)	12/1/2014	25	ND	LT20	43	53	118	6.4	Y	JTX-4049.0028
16-3088	45L	Suite C (Skid 200)	6/8/2016	25	ND	25	35	53	110	6.5	Y	JTX-4049.0033
16-3089	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	34	54	111	6.5	Y	JTX-4049.0032
16-3090	45L	Suite C (Skid 200)	6/8/2016	25	ND	LT20	36	54	114	6.5	Y	JTX-4049.0034
18-P009	45L	Suite C (Skid 100 and 200)	6/4/2020 2018	25	LT20	28	42	58	116	6.5	Y	JTX-4049.0051 DTX-2512.23
18-P004	45L	Suite C (Skid 100 and 200)	6/5/2020 2018	25	LT20	28	40	56	111	6.5	Y	JTX-4049.0052 DTX-2512.23
18-P003	45L	Suite C (Skid 100)	10/29/2020 2018	25	LT20	28	48	62	127	6.5	Y	JTX-4049.0053

DTX-3111

HIGHLY CONFIDENTIAL

DTX-3111.1

DTX-3111

PDX-7.83

Validity FOFCOLs ¶¶ 196-198

There Was No Inequitable Conduct

Allegedly Withheld 6-Month Data Is ***Not Prior Art***

Eight "45L -Swindon Batches"

Table 1 Batch Summaryto Support EXPAREL, 13.3 mg/mL Manufactured at Patheon

Table	Batch No.	Skid	Date of manufacture	Batch Size	Use of Batch	Storage Condition	Study Status
2	037188	300	13 Apr 2017	45 L	Registration, Stability	5ºC	15 months
3						25ºC	Completed
4	037189	300	19 Apr 2017	45 L	Registration, Stability	5ºC	15 months
5						25ºC	Completed
6	037190	300	21 Apr 2017	45 L	Registration, Stability	5ºC	15 months
7						25ºC	Completed
8	037191	400	09 May 2017	45 L	Registration, Stability	5ºC	15 months
9						25ºC	Completed
10	037192	400	11 May 2017	45 L	Registration, Stability	5ºC	15 months
11						25ºC	Completed
12	037193	400	15 May 2017	45 L	Registration, Stability	5ºC	15 months
13						25ºC	Completed
14	047903	300 & 400	17 May 2017[1]	4 x 45 L	Registration, Stability	5ºC	15 months
15						25ºC	Completed
16	126837	300	14 Dec 2016	45 L	Bioequivalence	5ºC	18 months
17						25ºC	Completed

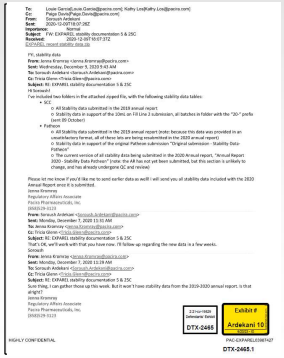
Q. And because they were not sold, you understand that these lots are not prior art?

A. I do understand that, yes.

Dr. Anna Schwendeman
trial transcript at
516:16-18.

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C) of 45 L Exparel before 1/22/21

Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
						0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
1	037188	45L	Skid 300 at Patheon	4/13/2017	25	ND	23	35	46	90	6.7	N	JTX-4049.0037
2	037189	45L	Skid 300 at Patheon	4/19/2017	25	ND	25	35	46	89	6.8	N	JTX-4049.0038
3	037190	45L	Skid 300 at Patheon	4/21/2017	25	ND	LT20	33	45	83	6.8	N	JTX-4049.0039
4	037191	45L	Skid 400 at Patheon	5/9/2017	25	ND	ND	35	44	80	6.9	N	JTX-4049.0040
5	037192	45L	Skid 400 at Patheon	5/11/2017	25	ND	ND	35	43	80	6.9	N	JTX-4049.0041
6	037193	45L	Skid 400 at Patheon	5/15/2017	25	ND	ND	35	42	78	6.9	N	JTX-4049.0042
7	047903	45L	Skid 300 and 400 at Patheon	5/17/2017	25	ND	25	34	43	79	6.8	N	JTX-4049.0043 DTX-2512.20
8	126837	45L	Skid 300 at Patheon	12/14/2016	25	ND	LT20	35	41	102	6.6	N	JTX-4049.0036 DTX-2519.1



DTX-2465 ("Ardekani Data");
see also DTX-3110

Allegedly Withheld 1-, 2-, and 3-Month Data Is ***in the Patent***

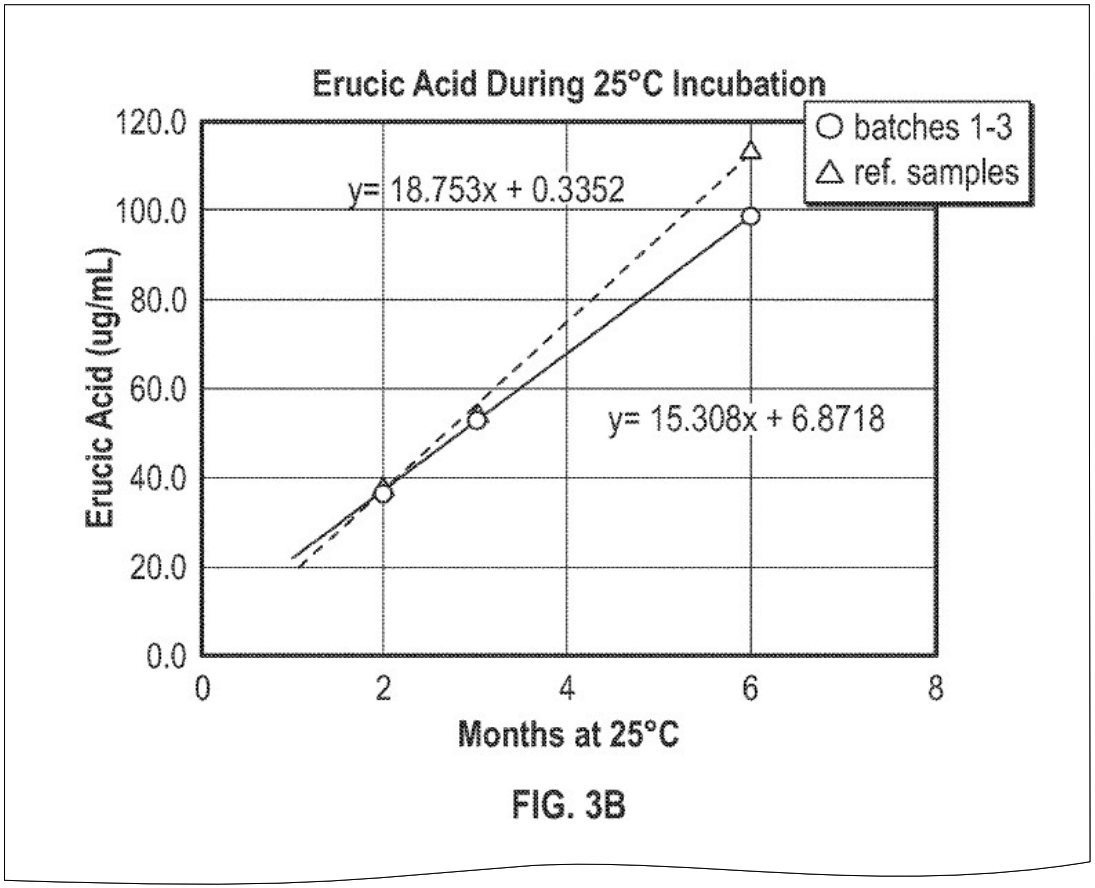


FIG. 3B

JTX-4121.0010

There Was No Inequitable Conduct

Roadmap

- Ms. Los and Dr. Dai did not withhold material 1-, 2-, and 3-month stability data
  - It's disclosed in the patent – cumulative
  - Primary Examiner Washville allowed the claims based on 6-month stability
- Ms. Los and Dr. Dai did not withhold material 6-month stability data
  - It's not prior art and therefore cannot be material
  - No evidence at trial that ***any*** Swindon 45L batches are prior art
  - No evidence at trial that Dr. Dai was aware of the Swindon 45L batches
- Ms. Los and Dr. Dai did not misrepresent data to the PTO
  - Ms. Los's testimony is corroborated and unrebutted
- Ms. Los and Dr. Dai did not intend to deceive the PTO
  - Intent to deceive is not a reasonable inference, let alone the ***only*** reasonable inference

Defendants' Inequitable Conduct Accusations Before Trial vs. After Trial

Dr. Jane Dai
Anthony Molloy
Kathy Los
Soroush Ardekani
Louie Garcia
Jeff Hall
Dr. John Grigsby
Paige Davis

ECF No. 298, Tab 10 at ¶¶371-481

Dr. Jane Dai

Kathy Los

Therasense Raised the Bar to Prove Inequitable Conduct

- "This court now tightens the standards for finding both intent and materiality in order to redirect a doctrine that has been overused to the detriment of the public." *Therasense Inc. v. Becton Dickinson & Co.*, 649 F.3d 1276, 1290 (Fed. Cir. 2011) (en banc).

- "This court does not adopt the definition of materiality in PTO Rule 56 . . . because reliance on [Rule 56] has resulted in the very problems this court sought to address by taking this case en banc." *Id.* at 1293-94.

- Defendants must prove by clear and convincing evidence that an individual involved in patent prosecution misrepresented or omitted material information with the specific intent to deceive the patent office. *Id.* at 1287.

But-For Materiality Is Required

- "A **prior art** reference is 'but-for' material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324, 1334 (Fed. Cir. 2012) (quoting *Therasense*, 649 F.3d at 1291).
- Data that is cumulative of what is disclosed in the patent cannot be material. *Regeneron Pharms., Inc. v. Merus N.V.*, 864 F.3d 1343, 1350 (Fed. Cir. 2017).

1-month Data Is in the Specification – Unasserted Claim 1

wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25° C. for one month.

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (µg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

45-L Process

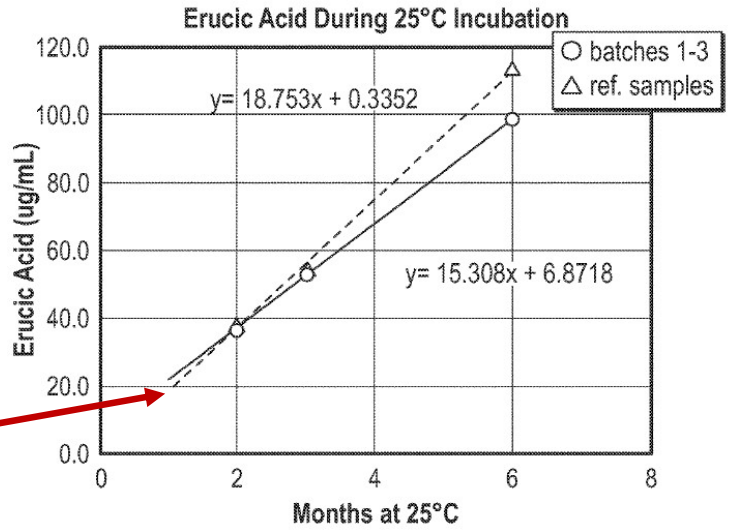


FIG. 3B

JTX-4121.0023, -.0021, -0010

See also Tr. at 171:8-174:17) (Dr. Grigsby explaining Fig. 3B and extrapolation); 755:14-757:1 (Dr. Klibanov explaining Fig. 3B and extrapolation)

Mr. Slifer Agrees the 1-Month Data Can Be Determined from Fig. 3B

Q. Let's start with the equation on top. If we set the X equal to 1 and add the numbers, I get 19.0882.

Does that sound right to you?

A. That sounds about right, yes.

Q. And the equation is -- that equation on top is for the dash line; is that correct?

A. My understanding is that corresponds to the best fit line with the dash line, yes.

Q. Thank you, sir.

Now, let's go to the equation on the bottom. If I said the X equal to one and add the numbers up, I get 22.1798.

Does that sound right to you?

A. It sounds about right.

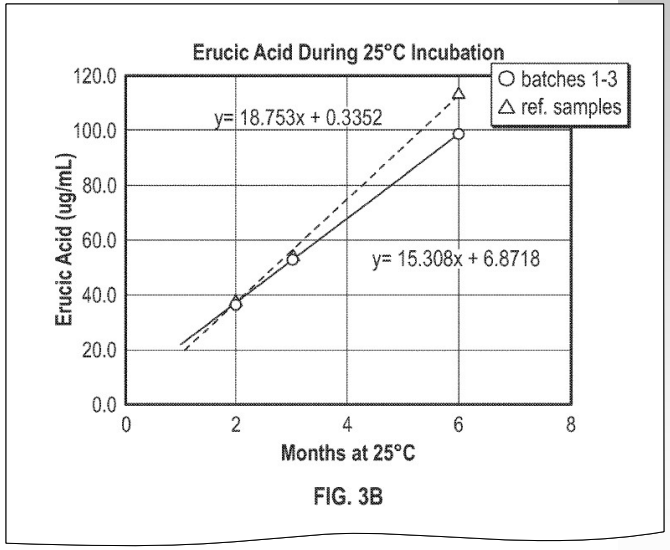


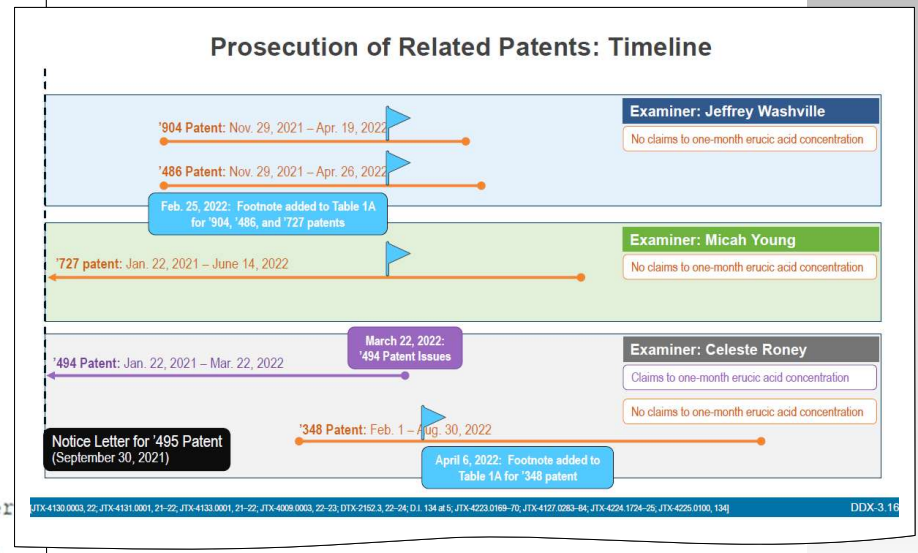
FIG. 3B

Russell Slifer
trial transcript at
668:8-20

JTX-4121.0010

Three Primary Patent Examiners Agreed: The Clarification to Table 1A Did Not Add "New Matter"

Q. And you refer on this slide to five Pacira patents, four of which had a footnote added to Table 1A during patent prosecution, right?
A. Yes.
Q. Okay. And those four are the ones with the little blue flag, right?
A. Yes.
Q. Okay. That's the '904 patent, the '486 patent, the '727 patent, and the '348 patent, right?
A. Yes.
Q. Okay. And that footnote to Table 1A was added to applications before three different examiners, Primary Examiner Washville, Primary Examiner Young, and Primary Examiner Roney; is that right?
A. Yes.
Q. Okay. And none of those primary examiners made a new matter objection when that footnote was added; is that right?
A. I didn't see anything in the record that would indicate that, no.



Russell Slifer
trial transcript at 669:7-25

DDX-3.16
(Slifer's Demonstratives)

n/a: At the 1 month time point, several batches of the reference samples contained erucic acid at concentrations below the lower limit of detection of the assay (20 µg/mL). Therefore, an average value of erucic acid concentration for all batches of the reference samples could not be calculated at the 1 month time point.

JTX-4225.0134; Tr. 828:18-831:4 (Mr. Godici explaining "new matter").

2- and 3-Month Data Is in the Specification – Unasserted Claims 3 and 5

3. The composition of claim **1**, wherein the erucic acid concentration in the composition is about 38 μg/mL or less after the composition is stored at 25° C. for two months.

5. The composition of claim **1**, wherein the erucic acid concentration in the composition is about 54 μg/mL or less after the composition is stored at 25° C. for three month.

JTX-4121.0023, -.0021, -.0010

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

Batch	Erucic acid concentration (μg/mL) 1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

45-L Process

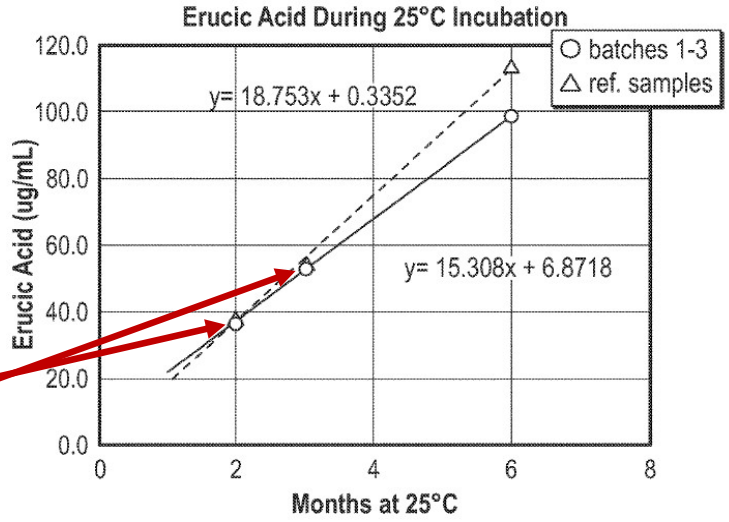
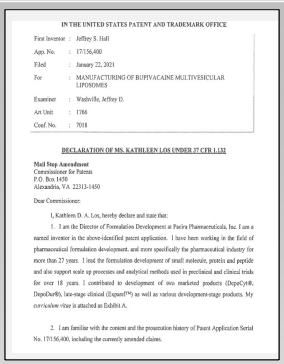


FIG. 3B

1-, 2-, and 3-month Stability Is not Material Because Allowance Based on 6-month Stability

4. The present application is directed to a 200L commercial scale manufacturing of bupivacaine multivesicular liposomes (MVLs), a project which we started developing in 2013. This new commercial process yields a bupivacaine MVL composition with superior stability as compared to the product made by the prior process. In particular, the bupivacaine MVLs composition prepared by the new process has demonstrated less lipid membrane degradation, by measuring a lipid degradation byproduct erucic acid in the bupivacaine MVLs suspension over a period of 6 months at 25°C. Erucic acid is a degradation product of dierucoyl phosphatidyl

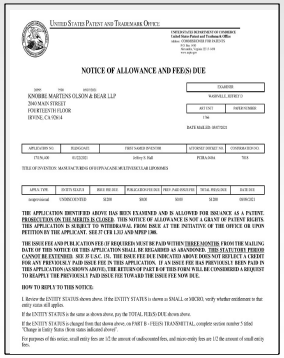
8. The following is an examiner's statement of reasons for allowance: The declaration of Ms. Los attests that the method claims as amended are not obvious in view of the teachings of Camu in view of Li. The prior art fails to teach the claimed degradation product of erucic acid after 6 months storage at 25C. Furthermore the combined art does not teach the claimed concentration of bupivacaine. The Office finds the declaration persuasive that the combined prior art does not teach the claimed method of preparation of MVL having the claimed storage stability.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION OF MS. KATHLEEN LOS UNDER 37 CFR 1.132

JTX-4001.2179
(Kathy Los Decl.)



NOTICE OF ALLOWANCE AND FEE(S) DUE

JTX-4001.2311

Inequitable Conduct FOFCOLs ¶¶ 388-402

PACIRA

Primary Examiner Washville Got it Right

Q. So in your view, Mr. Godici, Claim 1, which recites a limitation only to one-month erucic acid concentration, was allowed because of differences at the six months timepoint?

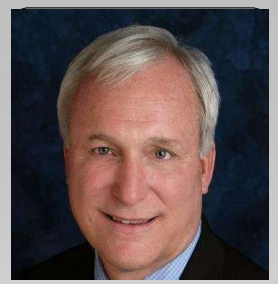
A. Well, it -- I might agree, but really, it's the patent office that says that. It's clearly in the record. The examiner says it here. So that's the position of the patent office with respect to why the claims were allowed.

Q. So please explain this to us, Mr. Godici. As a matter of patent office practice and procedure, did the patent examiner make a mistake in doing this?

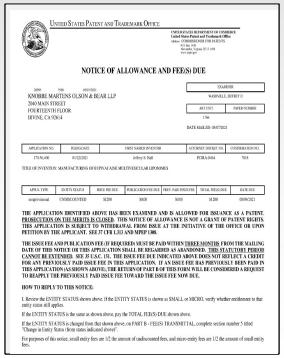
A. No. The way I see it, the process for examining product-by-process claims was followed completely. There was -- there was a prime facia case made of unpatentability, Camu and Li; then the burden shifted to the applicant to explain what the differences were between the product from the prior process and the product from the new process that came in via arguments from the patent attorney and the declaration that the examiner asked for.

Once that came in, the examiner says, "I understand, I -- the declaration is persuasive, and this is why I'm allowing the patent based on the six-month storage stability."

8. The following is an examiner's statement of reasons for allowance: The declaration of Ms. Los attests that the method claims as amended are not obvious in view of the teachings of Camu in view of Li. The prior art fails to teach the claimed degradation product of erucic acid after 6 months storage at 25C. Furthermore the combined art does not teach the claimed concentration of bupivacaine. The Office finds the declaration persuasive that the combined prior art does not teach the claimed method of preparation of MVL having the claimed storage stability.



Nick Godici
trial transcript at 842:14-843:9



NOTICE OF ALLOWANCE AND FEE(S) DUE

JTX-4001.2311

Defendants Re-Write the Examiner's Reasons for Allowance

"The Examiner's reference to 'erucic acid after 6 months' in the Notice of Allowance [] should be read…to mean all timepoints, not just the six-month timepoint."

- Defendants' Reply at 4.

Q. Now, you agree, Mr. Slifer, that examiners are trained that "where specific reasons are recorded by the examiner, care must be taken to ensure that statements for the reasons for allowance or indication of allowable subject matter, are accurate, precise, and do not place unwarranted interpretations, whether broad or narrow, upon the claims."

Do you see that?

A. Yes.

Q. And patent examiners are trained on that; is that right?

A. Yes.

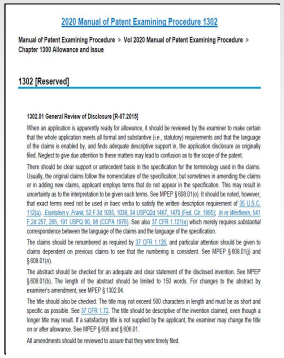
Q. Now, so you agree that patent examiners are trained to be careful when they write the reasons for allowance?

A. They're trained by the MPEP as this is, yes, to be accurate.

Q. And when Primary Examiner Washville allowed the '495 patent, he gave his reasons for allowance, correct?

A. He did set forth reasons, yes.

Russell Slifer
trial transcript at 673:22-674:13



2020 Manual of Patent Examining Procedure 1302

Manual of Patent Examining Procedure > Vol 2020 Manual of Patent Examining Procedure > Chapter 1300 Allowance and Issue

1302 [Reserved]

1302.01 General Review of Disclosure [R-07.2015]

DTX-2571.9-.10
MPEP Ch. 2020

6 Month Data: Non-Prior Art Is Not Material

- The "45-liter Swindon Batches" were not sold and therefore, ***are NOT*** prior art. (Schwendeman Tr. at 514:16-19, 515:21-24, 516:13-18 discussing PTX-492; DTX-2465.3)
- *Belcher's* "but-for" material information was ***prior art*** (450 F. Supp. 3d 512, 535, 542 (D. Del. Mar. 31, 2020))
  - *JHP's Adrenaline Product (**Sold, and Stipulated as "Prior Art"**)*
  - *Sintetica's Epinephrine Product*
  - *Stepensky Reference (Printed Publication)*
- *Merus's* "but-for" material information was ***prior art*** (144 F. Supp. 3d 530, 571-74 (S.D.N.Y. Nov. 2, 2015))
  - *Bruggemann Reference (Printed Publication)*
  - *WIPO Patent No. WO 91/00906 (Printed Publication)*
  - *Taki Reference (Printed Publication)*
  - *Zou Reference (Printed Publication)*
- **'"[P]rior art references, by definition, must be publicly available.' Therefore, [patentee] was not under any duty to disclose its internal documents**." *C.R. Bard, Inc. v. Medical Components, Inc.,* 2019 WL 1746309, *4 (D. Utah 2019) (dismissing IC allegation as not well-pleaded for relying on patentee's internal documents that were not prior art).

"45-L Swindon Batches" Among Ardekani Data Were Not Sold and Are Not Prior Art

Eight "45L -Swindon Batches"

Table 1 Batch Summaryto Support EXPAREL, 13.3 mg/mL Manufactured at Patheon

Table	Batch No.	Skid	Date of manufacture	Batch Size	Use of Batch	Storage Condition	Study Status
2	037188	300	13 Apr 2017	45 L	Registration, Stability	5°C	15 months
3						25°C	Completed
4	037189	300	19 Apr 2017	45 L	Registration, Stability	5°C	15 months
5						25°C	Completed
6	037190	300	21 Apr 2017	45 L	Registration, Stability	5°C	15 months
7						25°C	Completed
8	037191	400	09 May 2017	45 L	Registration, Stability	5°C	15 months
9						25°C	Completed
10	037192	400	11 May 2017	45 L	Registration, Stability	5°C	15 months
11						25°C	Completed
12	037193	400	15 May 2017	45 L	Registration, Stability	5°C	15 months
13						25°C	Completed
14	047903	300 & 400	17 May 2017[1]	4 x 45 L	Registration, Stability	5°C	15 months
15						25°C	Completed
16	126837	300	14 Dec 2016	45 L	Bioequivalence	5°C	18 months
17						25°C	Completed

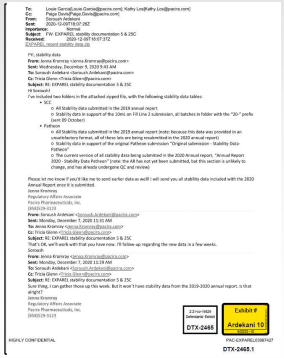
Q. And because they were not sold, you understand that these lots are not prior art?

A. I do understand that, yes.

Dr. Anna Schwendeman
trial transcript at
516:16-18.

Erucic Acid Concentration & pH in Accelerated Stability Testing (25°C) of 45 L Exparel before 1/22/21

Row	Batch	Batch Size	Mfr Site	Batch Mfr Date	Temp. (°C)	Erucic Acid (µg/mL)					pH (external)	Commercially Sold	Exhibit #(s)
						0 mo.	1 mo.	2 mo.	3 mo.	6 mo.	6 mo.		
1	037188	45L	Skid 300 at Patheon	4/13/2017	25	ND	23	35	46	90	6.7	N	JTX-4049.0037
2	037189	45L	Skid 300 at Patheon	4/19/2017	25	ND	25	35	46	89	6.8	N	JTX-4049.0038
3	037190	45L	Skid 300 at Patheon	4/21/2017	25	ND	LT20	33	45	83	6.8	N	JTX-4049.0039
4	037191	45L	Skid 400 at Patheon	5/9/2017	25	ND	ND	35	44	80	6.9	N	JTX-4049.0040
5	037192	45L	Skid 400 at Patheon	5/11/2017	25	ND	ND	35	43	80	6.9	N	JTX-4049.0041
6	037193	45L	Skid 400 at Patheon	5/15/2017	25	ND	ND	35	42	78	6.9	N	JTX-4049.0042
7	047903	45L	Skid 300 and 400 at Patheon	5/17/2017	25	ND	25	34	43	79	6.8	N	JTX-4049.0043 DTX-2512.20
8	126837	45L	Skid 300 at Patheon	12/14/2016	25	ND	LT20	35	41	102	6.6	N	JTX-4049.0036 DTX-2519.1



DTX-2465 ("Ardekani Data");
see also DTX-3110

Specific Intent to Deceive is Required

- "[T]he accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it." *Therasense,* 49 F.3d at 1290.
- "A finding that the misrepresentation or omission amounts to gross negligence or negligence under a 'should have known' standard does not satisfy this intent requirement." *Id.*
- "Intent and materiality are separate requirements. A district court should not use a 'sliding scale,' where a weak showing of intent may be found sufficient based on a strong showing of materiality, and vice versa." *Id*.

Intent to Deceive Must Be the ***ONLY*** Reasonable Inference

- "[W]hen there are multiple reasonable inferences that may be drawn, intent to deceive cannot be found."
  - *Therasense,* 49 F.3d at 1290.

Ms. Los Had No Intent to Deceive in Selecting Data for the ’495 Patent

Q. Ms. Los, was it convenient to use the same lots for the erucic acid stability data in table 1A of the '495 patent and the prefilled syringe stability study?

A. Yes, it was because the lots that were used for the prefilled syringe study met minimum criteria for a number of data points with measurable erucic acid.
And those were the same criteria we needed to make the comparison for table 1A. And therein lies the convenience, that we had already gone through the exercise of looking to see which lots had enough data to make that comparison.

Q. Did you understand, Ms. Los, that EXPAREL manufactured prior to 2016 was also prior art to your patent?

A. I did not.

When you testified earlier that the duty of candor includes not withholding data that is relevant to what the patent is about, is your understanding that that includes internal data about prior art commercial products?

A. I'm -- yeah, I guess not. At least, not to the scope I -- full scope.

Q. Sorry, what do you mean by "I guess not"?

A. Well, as I've tried to explain, our role -- my role and the role of my colleagues in the formulation development group has been to perform the analyses accurately, provide the data in full. With regard to understanding of the rules surrounding what does or doesn't get included, we count on our patent prosecution attorneys to make those interpretations.

Kathy Los

JTX-4289 at 165:3-15, 191:19-192:14, 267:2-8,

Ms. Los Used "N/A" to Avoid "Inventing Numbers"

Lot	0	1m	2m	3m	6m
20-3066	ND	28	35	52	NA
20-3067	28	41	57	75	NA
20-4076	27	43	59	70	NA
16-p004-pool	ND	LT 20	36	51	111
16-3088-200	ND	25	35	53	110
16-3089-200	ND	LT 20	34	54	111
16-3090-200	ND	LT 20	36	54	114
17-3142	LT 20	29	43	58	114
17-4135	LT 20	25	39	54	109
17-4136	LT 20	34	48	64	123
		28.3	38.7	55.4	113.1
		26.2	24.3	15.0	4.2

Q. What did you do with the LT 20 entries when calculating the average?

A. The Excel formula would ignore those.

Q. Did you make any attempt to correct for the fact that the Excel formula was ignoring the LT 20s?

A. Unfortunately, there's no way to do that. I mean, you can't -- you can't correct mathematically for it.

Q. Would it be possible to calculate an upper limit on the average by assuming that each of those values was 20?

A. I mean, that would be possible, but I would not do that.

Q. Why not?

A. Because I would be inventing numbers.

A. The true average can only be calculated from those lots that have data for them.

Q. So your stance, Ms. Los, is that by removing all of the low values, you can accurately calculate the average?

A. No, I'm not saying that -- I don't know. There's no good way of handling the data when you don't have reportable numbers for some of your data points. I mean, you have -- you have to settle on what is the best way without inventing data and that's what we did.

TABLE 1A

Erucic acid concentration in the bupivacaine MVLs as a functional of time

	Erucic acid concentration (μg/mL)			
Batch	1 month	2 months	3 months	6 months
1	22	36	54	99
2	23	38	51	99
3	23	38	54	98
Average	22.7	37.3	53.0	98.7
% RSD	2.5	3.1	3.3	0.6
Reference samples				
Average	n/a	38.7	55.4	113.1
% RSD	n/a	24.3	15.0	4.2

Kathy Los

JTX-4289 at 127:15-128:08, 129:3-7, 129:11-16; JTX-4037.0018

See also Dai Tr. JTX-4288 at 110:17-115:03 (testifying that Ms. Los's spreadsheet is the basis for Table 1A); *Id*. at 61:14-63:13 (testifying that Ms. Los provided Fig. 3B to Dr. Dai)

Defendants Cannot Ask the Court to Infer Intent Through Their Evidentiary Failures

- "[T]he 'patentee need not offer any good faith explanation unless the accused infringer first ... prove[s] a threshold level of intent to deceive by clear and convincing evidence.' The absence of a good faith explanation for withholding a material reference does not, by itself, prove intent to deceive."
  - *Therasense,* 49 F.3d at 1291 (citations omitted).
- Defendants ***never asked*** Ms. Los why she didn't rely on the unsold, non-prior art 2016/2017 Swindon 45L batches ("Ardekani Data")
  - No evidence in the record of a ***single*** Swindon 45L batch sold before 2020
- Defendants ***never asked*** Ms. Los how she interprets Fig. 3B, or why she extrapolated to one month
  - Ms. Los freely admitted ***at least five times*** that she was aware of 45L lots with lower 1-month erucic acid than 200L lots (JTX-4289 at 169:20-170:02; 216:12-217:10; 218:23-219:13; 250:14-251:01; 254:05-254:19)

Ms. Los Believed the Statements in Her Declaration to Be True

Q. When you signed this document, Ms. Los, did you understand that false statements to the patent office could jeopardize the validity of any resulting patent?

A. Yes.

Q. When you signed this declaration, you were aware that some batches of 45-liter EXPAREL had at least as good stability after one month as the 200-liter batches; correct?

A. The patent speaks to differences in the stability trends. That is to say the rate of hydrolysis as shown in one of the plots that I don't remember the number right now. So superior stability referred to here is the trend over time of the totality of the data of the 200-liter versus 45-liter.

When you told the patent office that the new process yields a composition with superior stability, were you aware that several batches of the 49-liter product had superior one-month stability to the 200-liter batches?

A. I mean, I was aware at the one-month time point that some of the 45-liter lots had erucic acid levels less than 20, which is lower than the number reported in this claim. That does not contradict the statement in the declaration, which in my mind, refers to the trajectory of that erucic acid level over time, not an absolute number at an early time point.

Kathy Los

JTX-4289 at 215:5-9; 216:12-217:4, 218:23-219:13

See Cornell Univ. v. Illumina, Inc., 2017 WL 89165 at *11 (D. Del. 2017) ("The inventor's belief that the declaration was true when submitted to the PTO further negates any inference of an intent to deceive the PTO."), citing *Vita–Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1332 (Fed. Cir. 2009) (no deceptive intent where inventor "believed the statement to be true at the time that he made it").

Dr. Grigsby Gave Live Testimony Consistent with Ms. Los's

- "Pacira relies exclusively on Ms. Los's ***implausible*** excuse that she understood 'improved stability' to refer to 'the trend over time of the totality of the data of 200-liter versus 45-liter,' and that Dr. Dai relied on Ms. Los's 'belief.'"
  - – Defendants' Reply at 10 (citing ***nothing***).

Dr John Grigsby
trial transcript at 171:8-15

Q. Let's go to Figure 3B of the '495 patent. Is the erucic acid data depicted in Figure 3B the same erucic acid data we just saw in Table 1A?

A. Yeah, it's just plotted on a graph.

Q. What is the purpose of plotting it on a graph?

A. This is really the appropriate way to evaluate stability data because now we can really evaluate the trends and you can see how erucic acid levels change over time.

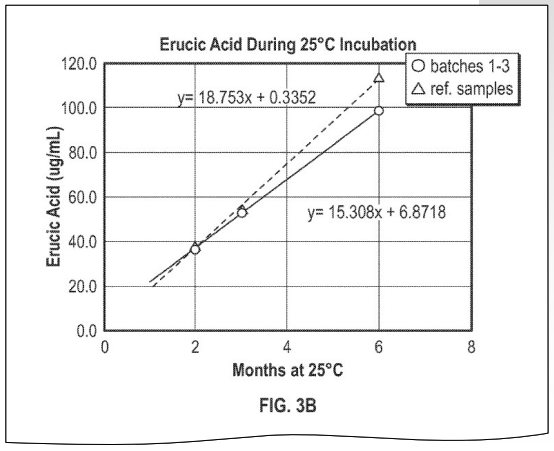
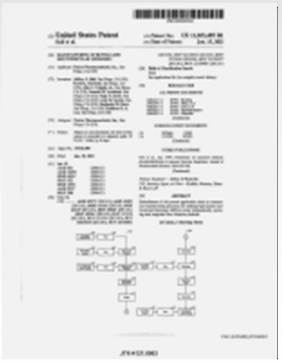


FIG. 3B



JTX-4121.0010

Dr. Dai Relied On Ms. Los, and Thus Could Not Have an Intent to Deceive

Q. Other than -- well, who drafted the figures in the '495 patent?

A. I know for figure 3A, 3B, and 3C, was provided to us by Kathy Los.

Q. Do you see that Exhibit 7 is an Excel spreadsheet?

A. Yes.

Q. Ms. Los writes, [As read] Hi, Jane, Daniel, I've also attached an updated version of the spreadsheet that contains -- and there are some privilege redactions -- and internal [lysine] and [dextrose].
Do you see that?

A. Yes.

Q. Is the data in this spreadsheet the basis for the data tables in the asserted patents?

A. Yes.

Q. Is this 45-liter data the data underlying the reference samples reported in table 1A of the asserted patents?

A. Yes.

Q. When you submitted this patent application to the patent office, Dr. Dai, was your understanding of the scope of the claims informed by conversation with anyone at Pacira?

A. Yes.

Q. Who, at Pacira, provided information that informed your understanding of the scope of this claim during prosecution?

A. Kathy Los and maybe additionally -- (Reporter clarification.)

A. Maybe additional inventors listed on the face of the '495 patent.

Dr. Jane Dai

JTX-4288 at 61:14-63:13; 110:21-111:2, 114:6-8, 115:1-3, 127:15-128:08

See Freshbub, Inc. v. Amazon.com, Inc., 93 F.4th 1244, 1254 (Fed. Cir. 2024) (affirming lack of intent to deceive where prosecution counsel believed the intent of another).

Unhappy with the Testimony, Defendants Attack Credibility

- Defendants offer no reason why Ms. Los or Dr. Dai would lie.
  - Ms. Los is a senior scientist on the verge of retirement (JTX-4289, Tr. at 273:12-14.)
  - No evidence of what she had to gain by '495 patent's issuance

- Dr. Dai is outside prosecution counsel.
  - Why would she would put her license at risk?
    - Implausible suggestion that she lies for all clients with important applications (Defendants' FOF 480)

Kathy Los

Dr. Jane Dai

The Scope of the ANDA Governs; Can't Shrink ANDA Scope without Amending the ANDA

- "What a generic applicant asks for and receives approval to market, if within the scope of a valid claim, is an infringement. See Abbott, 300 F.3d at 1373 ("[b]ecause drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry."). **If it had no intent to infringe, Reddy should not have requested, or should not accept, approval to market a product within the scope of the claim**."
  - *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1279 (Fed. Cir. 2013)

Amgen v. Sanofi Enablement Focused on Molecules

- *Amgen* represents a new world of enablement for ***chemical entities***
- "Amgen ***seeks to monopolize an entire class of things defined by their function*** . . . . It freely admits that it seeks to claim for itself an entire universe of antibodies." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 613 (2023).
  - Claim 7 here is not "functional"
- Court found Amgen patent "amount[s] to little more than [] research assignments" because:
  - "[C]reate a wide range of candidate antibodies and then screen each to see which happen to bind to PCSK9 in the right place and block it from binding to LDL receptors."
  - "[M]ake substitutions to the amino acid sequences of antibodies known to work and then test the resulting antibodies to see if they do too—an uncertain prospect given the state of the art." *Id.* at 614.

Pacira Changed the Mixing Speed to Meet the Particle Size Quality Parameter

Q. Because there are concerns about this d90 particle size, you had to change the mixing speed for the second emulsion step, right?

A. That's right.

Q. For these registration batches here, those batches used a speed at 450 RPM for the second emulsion step, right?

A. I believe that's true.

Q. And you changed the speed to 495 RPM for subsequent batches; is that right?

A. Eventually, we did.

Jeff Hall
trial transcript at
135:5-11; 35:20-136:4

Pacira Changed the Mixing Speed to Meet the Particle Size Quality Parameter

Q. You understand that even today, Pacira can't routinely get 200-liter product that meets the erucic acid concentrations, right?

A. Well, my understanding is that this is because they also pursue other objectives, such as the particle size. So they have other objectives that they have to pursue in their experimentation. That's my understanding of his testimony.

Q. You understand that today, Pacira can't actually routinely get the 200-liter process to meet the erucic acid limitations of Claim 7, right?

A. I wouldn't say "can't." I would say "doesn't."

Dr. Alexander Klibanov
trial transcript at
814:5-15